AstraZeneca

Non-Interventional Study (NIS) Report	
NIS Name/Code	NIS-NIT-DUM-2010-1
Edition Number	<<>>
Date	28-01-2013

A non-interventional study to Investigate the ratio of Mis-diagnosed bipolar symptoms in Patients diagnosed as with treatment Resistant major depressive disorder (MDD). IMPROVE Study.

Study dates	**First Subject In: 19/05/2011** **Last Subject Last Visit: 14/03/2012**

National/international Coordinating Investigator:	Mauro Carta, *Professor* *Psychiatric Department Director* via Liguria 13 09123 Cagliari *+39 335 499994 (mobile) mgcarta@tiscali.it (e-mail)*
MCMD / Delegate:	Dr.ssa Marianna Alacqua Medical Affairs Manager Neurosciences/Inflammation & Infection AstraZeneca SpAMedical Department AstraZeneca Italy Palazzo Volta – Via F. Sforza 20080 Basiglio (MI)

Study dates	**First Subject In: 19/05/2011** **Last Subject Last Visit: 14/03/2012**

Biostatistician: Daniela Garavaglia, *Head of Statistical Unit*
OPIS Palazzo Aliprandi
via Matteotti, 10
20832 Desio (MB)

This submission / document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object

LIST OF ABBREVIATIONS

CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
DM	Data Manager
FAS	Full Analysis Set
HCL-32	Hypomania Check List-32
MDD	Major Depressive Disorder
MDQ	Mood Disorder Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-Interventional Study
WHO-DRL	World Health Organization Drug Reference List

NIS REPORT SYNOPSIS (IF APPLICABLE)

Study Title: A non-interventional study to Investigate the ratio of Mis-diagnosed bipolar symptoms in Patients diagnosed as with treatment Resistant major depressive disorder (MDD). IMPROVE Study

Rationale

MDD (Major Depressive Disorder) is a common disorder and is a leading cause of disability worldwide (1-3), as measured by YLDs (Years Lived with Disability), and the 4th leading contributor to the global burden of disease (DALYs - Disability Adjusted Life Years) in 2000. By the year 2020, depression is projected to reach 2nd place of the ranking of DALYs calculated for all ages and both sexes (3).

Although there are several classes of antidepressant treatment, resistance is a major concern. According to the recent NIMH-funded Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, only 32.9% of patients achieved remission in level 1 with one SSRI (4).

The term “treatment-resistant depression” should be applied to patients who do not respond to at least two antidepressant treatment trials with drugs from different pharmacological classes given in an adequate dose for a sufficient duration (5-7).

The optimization of a treatment resistant depression requires a good knowledge of the conditions associated with resistance to antidepressants. One such important condition is the undiagnosed bipolarity among patients with depressive disorders, in particular the presence of hypomanic symptoms.

The use of instruments for assessing the hypomanic symptoms, such as the Hypomania/Mania Symptom Checklist (HCL-32) can increase the recognition of undiagnosed and therefore inadequately treated bipolarity as an important cause of drug resistance in depression diagnosed as unipolar.

HCL-32 was developed by Angst et al in 2005 and then translated in several languages, including Italian (8).

HCL-32 is a simple, self-administered, 32-item questionnaire that can provide important insights on unrecognized hypomanic symptoms in patients diagnosed as with MDD. A positive answer to at least 12 items is revealing of a possible hypomanic condition.

HCL-32 is not a diagnostic tool but it only gives information on underlying bipolarity.

In a recent study, Dudek et al (9) compared patients with treatment resistant MDD vs. patients without treatment resistant MDD, using HCL-32 as a tool to assess the presence of hypomanic symptoms.

They showed that significantly more treatment resistant patients had bipolarity features detected by HCL-32 in comparison with non-treatment resistant patients.

Objectives

(a) Primary objective

- To define the potential bipolarity status in treatment resistant MDD patient population by assessment of presence of hypomanic symptoms, in order to reduce diagnostic mistakes leading to outcome worsening.

(b) Main secondary objectives

- To collect patient characteristics by evaluation of demographic informations
- To collect disease characteristics by evaluation of the number of previous episodes, and the duration of current episode
- To collect information on the on-going treatments

Study design

This is a multicentre, non-interventional, single visit study.

The study only detected hypomanic symptoms in treatment resistant MDD patients by means of HCL-32 administration.

No efficacy and tolerability of pharmacological treatments were assessed.

Patients matching inclusion and exclusion criteria were consecutively enrolled; each investigator had to include the first 10 to 40 patients visited as treatment resistant MDD.

Target subject population

Patients with treatment resistant major depressive disorder were to be evaluated in order to assess the presence of hypomanic symptoms as cause of resistance.

Study variable(s):

- Primary variable

  -Hypomanic Symptom Check List (HCL-32), Italian version

- Other Variables

  - Patients demographics
  - Medical history
  - Medical treatment informations

Statistical methods

In accordance with the primary study objective, the estimation of sample size was based on the HCL-32 score in treatment resistant patients. The computation was referred to the comparison between the group of patients treatment resistant due to bipolarity and the group of patients treatment resistant due to other causes. From a previous study (9), the HCL-32 score in treatment resistant patients was expected to be 11.9±8.3. Assuming α=0.05 and β=0.10 (i.e. a power of 90%) and conducting a two-tailed t-test, a total of 660 patients was sufficient for detecting as statistically significant an absolute difference in the HCL-32 score of 2.1 (11.9 versus 14.0) between the two groups.

During the conduction of the study, it was noticed by the principal investigator that the proportion of HCL-32 positive subjects enrolled into the study could be greater than one expected. As a consequence, a descriptive evaluation of the distribution of HCL-32 total score in 199 out of 202 subjects present in database on 20th of February 2012 was performed and the proportion of HCL-32 positive subjects was equal to 58.29%. The mean total score in overall sample was 13.27 (min 0 max 29) with a standard deviation of 6.31.

The sample size of the study was consequently re-estimated and the number of patients enrolled on 29th February 2012 were shown to be sufficient for detecting as statistically significant an absolute difference in the HCL-32 score of 2.1 with α=0.05 and a power of almost 90%. For that reason on 14th March 2012 the enrolment was closed with a total of 446 patients enrolled.

All the statistical analyses were executed using the software SAS System version 9.2.

Patients were subsequently divided into two groups ccording to the total score of HCL-32: if the score was greater than or equal to 12, patients were assigned to group of patients with hypomanic symptoms. Otherwise, if the score was lower than 12, patients were assigned to group of patients without hypomanic symptoms.

All the recorded data and derived variables were summarized, overall (i.e. on all enrolled patients) and by group (i.e. on patients classified as with or without hypomanic symptoms), by means of the

descriptive statistics: mean, standard deviation, median, 25th and 75th percentile, minimum and maximum for continuous variables; absolute and relative frequencies for categorical ones.

A complete description of patient disposition overall and by group was provided, specifying the number of completed and discontinued patients with the reason for the discontinuation.

Primary efficacy analysis was performed on patients without missing data in the 32 items of HCL-32 used to compute total score (Complete Case population) on HCL-32 score computed as the sum of positive answers to the 32 items of the questionnaire.

The difference between the score means in the two groups was estimated together with 95% Confidence Interval. The study had to be considered as conclusive if the lower limit of the confidence interval for the difference in means lies above 0 points. A T test was also applied, computed with the Satterthwaite method for unequal variances, to prove the hypothesis of statistical difference between the two groups.

Some Sensitivity analyses were performed on HCL-32 score according to Best and Worst Scenario as well as to Prevalence approach to missing data imputation: the consistency of study results and conclusions were consequently evaluated.

Study Results

Twenty-nine centres, out of the 32 activated, enrolled a total of 446 patients: 256 (57.40%) belonged to the group with hypomanic symptoms, i.e. had a HCL-32 Total Score greater than or equal to 12, 185 (41.48%) belonged to the group without hypomanic symptoms, i.e. had a HCL-32 Total Score lower than 12. As already emerged during the evaluation done in course of the study, the proportion of HCL-32 positive subjects was confirmed to be greater than expected (43.9% of examined subjects).

Overall, 5 patients (1.12%) were not Group Defined (Patients 1115, 2003, 2804, 4013, 4204) since their missing data did not allow to classify them as belonging to the Hypomanic or Not Hypomanic Group.

441 patients (98.88%) were Group Defined, i.e. whose belonging to one group did not depend upon missing data. Out of these, 256 (58.05%) belonged to the group with hypomanic symptoms, 185 (41.95%) belonged to the group without hypomanic symptoms. A total of 420 patients (94.17%) were Completer Patients, i.e. without missing data in the 32 items of HCL-32, 242 (57.62%) belonged to the group with hypomanic symptoms, 178 (42.38%) belonged to the group without hypomanic symptoms.

In the total sample a mean age of 48.62±10.58 years was recorded, in the hypomanic group the mean age was 47.66±10.41 years while in the not hypomanic group the mean age was 49.84±10.67 years The difference between the two groups was statistically significant.

No difference in gender was recorded between the two groups.

In the Completer patients, primary efficacy population, the overall mean HCL-32 total score was 12.95±6.23: in the hypomanic group the mean was 17.34±3.87 while in the not hypomanic group the mean total score was 6.99±3.05; the difference in means was 10.35 with 95% CI of 9.69-11.01 (computed with Satterthwaite method for unequal variance groups). The null hypothesis of equality of the means was refused with a high level of statistical significance (p-value <0.0001 at T Test). Hypomanic patients had a HCL-32 total score higher than not hypomanic patients so confirming the reliability of the HCL32 as sensitive instrument for discriminating bipolar patients in major depressive patients treatment resistant

All the approaches applied to the sensitivity analyses, with the different imputations to missing data in the best and worst scenarios as well as in prevalence scenario, had only minimal influence on the results as regards the capacity of HCL-32 questionnaire to discriminate between hypomanic and non-hypomanic patients.

In the completers population “active/elated hypomania” and “irritable/risk-taking hypomania” sub-scores were respectively 8.01±4.90 and 2.53±1.95 overall. An high difference among the two groups was detected in the “active/elated hypomania”: the mean was 11.27±3.11 in the hypomanic group and 3.57±3.05 in the not hypomanic group. The “irritable/risk-taking hypomania” sub-score was instead more homogeneous.

According to the logistic regression model applied, the belonging to the group of hypomanic patients rather than to the not hypomanic group was detected to be significantly associated with age, professional status, elapsed time from the onset of the current episode and the presence of concomitant diseases or pathologies that could interfere on the depressive disorders.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDIX

1. STUDY SITES

Twenty-nine centres, out of the 32 activated, participated in this non interventional study.

The details of activated sites and principal Investigators are reported in the Appendix B and in first section of "Tables and Figures" document.

2. PUBLICATIONS

The results of this study will be summarized in a paper to be submitted to an international specialistic review.

3. STUDY DATES

First Subject In: 19/05/2011

Last Subject Last Visit: 14/03/2012

4. BACKGROUND AND RATIONALE

The purpose of this non interventional study is to evaluate one of the most important reasons of treatment resistance in patients with treatment resistant MDD: the presence of undetected hypomanic symptoms.

Patients with treatment resistant MDD have increased risk of relapse, increased chronicity of depressive episodes with shorter durations between episodes, and impairments in workplace performance and social function when compared with those who are treatment responder. They also have increased all-cause mortality and in particular higher risk of suicide (8).

Several factors predispose patients to treatment non response, including chronicity, comorbidity (mainly anxiety), and sub-threshold hypomanic symptoms.

There are several instruments for assessing the hypomanic symptoms, among them the most used are the Mood Disorder Questionnaire (MDQ) and the HCL-32. They can increase the recognition of undiagnosed and therefore inadequately treated bipolarity as an important cause of drug resistance in depression. HCL-32 seems to be more sensitive than MDQ in detecting hypomanic condition (9,10).

HCL-32 is a simple, self-administered, 32-item questionnaire that can provide important insights on unrecognized hypomanic symptoms in patients diagnosed as with MDD. A positive answer to at least 12 items is revealing of a possible hypomanic condition.

HCL-32 is not a diagnostic tool but it only gives information on underlying bipolarity.

Several authors used MDQ and HCL-32 to detect hypomanic symptoms in patients with treatment resistant MDD. In this population prevalence of MDQ -positive patients ranged between 13.6% (10) and 21.3% (11) of the examined subjects while, as reported in the large retrospective study by Dudek (10), the prevalence of HCL-32 positive patients was 43.9% in treatment resistant group and 30.05% in non treatment resistant.
HCL-32-positives were more often male, less educated, and reported more often co-morbid dysthymia, social phobia, generalized anxiety disorder and alcohol dependence. Severity of depressive symptoms was higher in HCL-32-positives and they had more often a history of serious suicide attempts.
Under-detection of hypomanic symptoms can cause diagnostic and therapeutic mistakes resulting in a more severe and complex form of illness. The use of HCL-32 can improve diagnosis and treatment of depressive disorders.

5. OBJECTIVES

The purpose of this non interventional study is to evaluate one of the most important reasons of treatment resistance in patients with treatment resistant Major Depressive Disorder (MDD): the presence of undetected hypomanic symptoms.

5.1 Primary Objective

- The primary objective of the study is to define the potential bipolarity status in treatment resistant MDD patient population by assessment of presence of hypomanic symptoms, in order to reduce diagnostic mistakes leading to outcome worsening.

5.2 Secondary Objective

Secondary objectives of the study are:

- To collect patient characteristics by evaluation of demographic informations.
- To collect disease characteristics by evaluation of the number of previous episodes, and the duration of current episode.
- To collect information on the on-going treatment.

6. STUDY DESIGN AND SELECTION CRITERIA

This is a multicentre, non-interventional, single visit study.

The study had to detect hypomanic symptoms in treatment resistant MDD by means of HCL-32 administration. Further re-evaluation of MDD diagnosis was not a direct aim of the study. No efficacy and tolerability of pharmacological treatments was assessed.

Figure 1: Study Flow Chart

In order to ensure that study collected information represented the real life clinical practice, selected study centres from each part of Italy that manage this population were involved; approximately a total of 30 centres had to enrol a total of 660 patients, 10 to 40 per site. Patients had to be consecutively included in temporal sequence.

Twenty-nine centres, out of the 32 activated, enrolled a total of 446 patients.

In Table 1 the information recorded in the visit 1 (only 1 visit) is reported.

Table 1 Study Plan

Visit	1
Informed consent	X
Medical history	X
Demography	X
Inclusion/exclusion criteria	X
Current medication	X
HCL-32	X

Patients diagnosed with MDD (documented in the medical record) visiting the investigator's site had to be invited to participate in this study, if eligible based on the following inclusion and exclusion criteria.

6.1 Inclusion Criteria

1. Written informed consent form

2. Male and Female age ≥18-65 ≤ years

3. Diagnosis of MDD according to DSM-IV TR (296.3 x Major Depressive Disorder, recurrent)

4. Treatment resistance defined as non-response to at least 2 antidepressants given in an adequate dose for a sufficient duration (following the specific SmPC), withlast antidepressant treatment on-going.

6.2 Exclusion Criteria

1. Patients already participating in clinical trial or any other interventional study

2. Patients unable to understand HCL-32 item meaning.

6.3 Treatments

This is a non-interventional study. The assignment of a subject to a therapeutic strategy had to be independent from the participation to NIS study and had to fall within the current clinical practice.

The evaluation of efficacy and tolerability of pharmacological treatments was not an aim of the study. However, information on antidepressant treatments was collected in order to define patients as treatment resistant and for descriptive purpose.

The following information was collected

- Trade name and generic name
- Dosage, form and strength

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

Adult patients with previous documented MDD diagnosis and treatment resistance, were enrolled in this study.

7.1 Sample Size Estimation

In accordance with the primary study objective, the estimation of sample size was based on the HCL-32 score in treatment resistant patients. The computation was referred to the comparison between the group of patients treatment resistant due to bipolarity and the group of patients treatment resistant due to other causes. From the previous study by Dudek (10) , the HCL-32 total score in treatment resistant patients was expected to be 11.9±8.3. Assuming α=0.05 and β=0.10 (i.e. a power of 90%) and conducting a two-tailed t-test, a total of 660 patients was sufficient for detecting as statistically significant an absolute difference in the HCL-32 score of 2.1 (11.9 versus 14.0) between the group of patients treatment resistant due to other causes and the group of patients treatment resistant due to bipolarity.

During the conduction of the study, it was noticed by the principal investigator that the proportion of HCL-32 positive subjects, defined as subjects with HCL-32 total score greater than or equal to 12, enrolled into the study could be greater than expected. As a consequence, a descriptive evaluation of the distribution of HCL-32 total score in 199 out of 202 subjects present in database on 20th of February 2012 was performed. The proportion of HCL-32 positive subjects was equal to 58.29%. The mean total score in the overall sample was 13.27 (min 0 max 29) with a standard deviation of 6.31.

The sample size of the study was consequently re-estimated taking into account a standard deviation of 6.31. The number of patients enrolled on 29th February 2012 were shown to be sufficient for detecting as statistically significant an absolute difference in the HCL-32 score of 2.1 with α=0.05 and a power of almost 90%. For that reason on 14th March 2012 the enrolment was closed with a total of 446 patients entered.

8. CRITERIA FOR EVALUATION (MAIN VARIABLES)

8.1 Primary variable

Hypomania Checklist 32 (HCL-32) was used to detect underlying bipolarity in treatment resistant patients diagnosed as with major depressive disorder.

This outcome variable was used as the basis for the sample size calculation, as reported in section 7.1.

8.2 Secondary variables

Patients demographics: the following variables were collected in order to describe the study population

- Gender
- Age
- Professional status
- Family status

Medical history: the following variables were collected in order to describe the medical history of this population

- Psychiatric diagnosis
- N° of previous episodes (from diagnosis) in the last year
- Onset Time of current episode
- Relevant disease/pathology that could interfere with this pathology /treatment

Medical treatment information: the following variables were collected in order to describe the information treatment

- Current treatment
- Previous last treatment

8.3 Patient Reported Outcomes (PRO)

The Hypomania Check List-32 (HCL-32) questionnaire, Italian version by Carta MG & Hardoy MC, to be filled in by the patients, was adopted.

The scale considered the following 32 items, in terms of presence / absence:

1. Ho bisogno di meno sonno
2. Mi sento più ricco di energia e più attivo
3. Mi sento più sicuro di me stesso
4. Mi piace di più il mio lavoro
5. Sono più socievole (faccio più telefonate, esco di più con gli altri)
6. Mi piace di più viaggiare e viaggio di più
7. Guido più velocemente o in modo più spericolato
8. Spendo molto/troppo denaro
9. Rischio di più (sul lavoro e nella vita di ogni giorno)
10. Sono più attivo fi sicamente (ad esempio faccio più sport)
11. Faccio più piani
12. Ho più idee, sono più creativo
13. Sono meno timido e inibito
14. Vesto abiti più colorati e stravaganti o mi trucco di più e in modo originale
15. Desidero incontrare più gente e la incontro
16. Sono più interessato al sesso, ho più desideri sessuali
17. Corteggio e mi faccio corteggiare di più o sono sessualmente più attivo
18. Parlo di più
19. Penso più velocemente
20. Faccio più battute o giochi di parole
21. Mi distraggo più facilmente
22. Faccio molte cose nuove
23. I miei pensieri saltano da un argomento all'altro
24. Tutto mi riesce più facile o più veloce
25. Sono più impaziente e qualche volte più irritabile
26. Posso essere eccessivo o irritante per gli altri
27. Litigo di più
28. Sono più ottimista
29. Bevo più caffè
30. Fumo di più
31. Bevo di più alcolici (vino, birra, liquori, amari, ecc.)
32. Prendo più farmaci o droghe (sedativi, tranquillanti, stimolanti, ecc)

The HCL-32 total score is computed as the sum of the positive (yes) answers.

8.4 Health Economic measurements and variables (if applicable)

Not applicable.

8.5 Safety Variables

Due to the non-interventional character of this study, no pro-active safety data collection had to take place.

9. STATISTICAL METHODS

9.1 Data Management

9.1.1 Data Collection

Data were entered in the CRF by the investigators. The Investigator was responsible for entering data into the CRF according to the Investigator Instructions Manual, provided to the site with data entry instructions.

A copy of the CRF had to be archived at the investigation's site.

The relative section of Data Management Plan included detailed information.

9.1.2 Database Management and Quality Control

The Monitor had to forward the original paper CRF pages to the Data Manager (DM) of CRO working on behalf of Astra Zeneca. The DM had to verify that the description of the documentation sent was complete and data accurately filled in.

The clinical database was implemented in Oracle Clinical (Oracle Pharmaceutical Applications Release 4.5).

For each field a specific variable was arranged according to the characteristics of the datum collected. Besides the variables listed in the CRF, the following derived variables were included into the database:

- MedDRA code for medical terms code-list;
- WHODRL codes for therapy code-list.

Double data entry was carried out into the database by DM. The Data Manager had to carry out only obvious corrections on the original data present in the CRF. All other discrepancies present

in the database were addressed in a Data Clarification Form ORACLE (DCF) issued to the site for resolution. A complete list of the checks applied to the database was kept in the Data Validation Document (DVD). The data validation procedures were programmed inside Oracle Clinical, except for some checks that were implemented in SAS program. In compliance with the Validation Procedure, the checks were carefully tested by the DM before the start of the cleaning activity. The list of post-entry checks was reported in the DVD. Inconsistencies arisen by the post-entry checks were clarified with the Investigator by queries only if the data were verified by the Monitor through the SDV. Obvious inconsistencies or discrepancies had to be resolved by the DM himself. Permitted obvious corrections were defined in the Obvious Corrections Document.

The database was considered clean after all queries had been solved, database corrections done, medical coding carried out and approved and no other inconsistencies were detected. All changes and editing of data entered in the clinical study database were logged by the Oracle audit trail facility.

9.2 Statistical and Analytical Plan

9.2.1 General Methodology

All the analyses were executed using the software SAS System version 9.2.

Patients were divided into two groups according to the total score of HCL-32 (see section "Primary efficacy variable"): if the score was greater than or equal to 12, patients were assigned to Group 1 (patients with hypomanic symptoms). Otherwise, if the score was lower than 12, patients were assigned to Group 2 (patients without hypomanic symptoms).

Only patients whose belonging to one group did not depend upon missing data in the 32 items of HCL-32 questionnaire used for computing the total score were classified as with or without hypomanic symptoms.

Sample characteristics description was provided for all enrolled patients. Patients were classified as with or without hypomanic symptoms if the belonging to one group did not depend upon missing data.

All the recorded data and derived variables were summarized, overall (i.e. on all enrolled patients) and by group (i.e. on patients classified as with or without hypomanic symptoms), by means of the descriptive statistics: mean, standard deviation, median, 25th and 75th percentile, minimum and maximum for continuous variables; absolute and relative frequencies for categorical ones.

A complete description of patient disposition overall and by group was provided, specifying the number of completed and discontinued patients with the reason for the discontinuation.

Medical history were described by System Organ Class and Preferred Term codified according to MedDRA dictionary, version 14. Previous and current antidepressive medication had to be

described by Preferred Term and ATC codes (level two) of the WHO-DRL dictionary, version Q4-2009.

Elapsed months from the onset of the current episode were computed as the number of elapsed days from the date of the onset of the current episode to the date of visit /30.5. For missing data in day and/or month of onset of the current episode the assumptions day=15 and/or month=6 were made.

In the analysis of treatment Switch in the Year previous to the study, for missing data in day and/or month of start/end of treatment the assumptions day=15 and/or month=6 were made.

Patients with an affirmative answer to the question in the HCL Questionnaire "Did the questions above, which characterize a high, describe how you are sometimes?" had to skip to the item "Compared to other people my level of activity, energy and mood". Patients with a negative answer to the question "Did the questions above, which characterize a high, describe how you are most of the time?" had to skip to the end of the questionnaire. Data have been reported only for patients that should have answered according to the questionnaire indications.

The length of the longest high was computed as months*30.5+days.

Normality of continuous variables was assessed by means of Shapiro-Wilk test.

All statistical tests were performed with a significance level α=0.05.

9.2.2 Efficacy Data

Primary efficacy analysis was performed on Complete Case population, that is patients without missing data in the 32 items of HCL-32 used to compute total score. (

Sensitivity analyses on primary efficacy endpoint were performed on population of group defined patients, i.e. whose classification in group with or without hypomanic symptoms did not depend upon missing data, as well on all enrolled patients.

Primary efficacy analysis

HCL-32 score is the primary efficacy variable; it was computed as the sum of positive answers to the 32 items of the questionnaire.

Descriptive statistics and graphical representation of HCL-32 score were provided overall and by group.

The difference between the score means in the two groups was estimated together with 95% Confidence Interval The study had to be considered as conclusive if the lower limit of the confidence interval for the difference in means lies above 0 points. A T test was also applied,

computed with the Satterthwaite method for unequal variances, to prove the hypothesis of statistical difference between the two groups.

Descriptive statistics and graphical representation were provided overall and by group also for two sub-scores each addressing one specific variant of hypomanic behaviour: “active/elated hypomania” and “irritable/risk-taking hypomania”.

The sub-scores included the following items:

- active/elated hypomania: items 2, 3, 4, 5, 6, 10, 11, 12, 13, 15, 16, 19, 20, 22, 24 and 28;

- irritable/risk-taking hypomania: items 7, 8, 9, 21, 25, 26, 27, 31 and 32.

Finally, descriptive statistics for each items of HCL-32 were provided overall and by group.

Handling of missing data

As reported above, the primary analysis was performed in the Complete Case population, considering only patients without missing data in the 32 items of HCL-32 used to compute the score.

The sensitivity analyses were performed excluding only patients with undefined group due to missing data for the 32 items of HCL-32 questionnaire used to compute the total score. The Best Scenario and the Worst Scenario were assumed for patients with missing values. In the first case missing values were replaced with affirmative answers, in the latter missing values were replaced with negative answers.

A Prevalence Approach was also applied: missing values in each patient were replaced by his/her proportion of positive answers in the filled items.

To illustrate the robustness of the conclusions, the above sensitivity analyses were performed for the primary efficacy variable, also on all enrolled patients.

Results emerging from a Best Scenario, a Worst Scenario and a Prevalence Approach had to be compared. In those analyses the number of patients included in the compared groups could vary.

The results had to be compared for consistency and if they lead to similar results this provide reasonable assurance that the lost information had no effect on the overall study conclusions.

Sample characteristics

Age at consent was described overall and by groups. Homogeneity of data was tested by means of a Wilcoxon Rank-sum test, as the data did not respect normality assumption.

For categorical variables (gender, professional and family status) descriptive statistics (absolute and relative frequencies) were presented. Chi-square test was used to test the association between

these categorical variables and the belonging to one of the two groups. With cell frequencies less than 5, Fisher exact test was adopted.

Absolute and relative frequencies were provided for psychiatric diagnosis overall and by group.

Descriptive statistics of time elapsed from the onset of the current episode and number of previous episodes in the last year were provided overall and by group. Homogeneity of data between groups was tested by means of the Wilcoxon Rank-sum test, as the data did not respect normality assumption.

Relevant disease/pathology that could interfere with this pathology/treatment were coded according the MedDRA dictionary and the incidence rates of diseases were described by System Organ Class and by Preferred Term by group and overall.

Absolute and relative frequencies of patients with at least one disease/pathology were provided. Chi-square test was used to test association with the belonging to one of the two groups.

Current treatment and previous last treatment were coded according to WHODRL dictionary and frequencies were provided by ATC and Preferred Term overall and by group.

Descriptive statistics of treatment switch in the last year were provided overall and by group. Absolute and relative frequencies of patients with at least one treatment switch were provided. Chi-square test was used to test association with the belonging to one of the two groups. With cell frequencies less than 5, Fisher exact test was adopted.

Secondary analysis

An explorative multivariate analysis was applied in order to investigate the effect of explicative factors (age, gender, family status, professional status, psychiatric diagnosis, time elapsed from the onset of the current episode, number of previous episodes in the last year, relevant disease/pathology that could interfere with this pathology/treatment and treatment switch) on hypomanic condition status, identified by HCL-32 questionnaire as defined above.

A logistic regression model including all the aforementioned variables had to be applied. Odds ratio and 95% CI were provided. The model had to be also fitted using a stepwise selection of variables.

9.2.3 Safety Data

Not applicable.

9.2.4 Interim Analysis

No interim analyses were planned.

9.3 Changes in the conduct of the study or planned analyses

During the conduction of the study, it was noticed by the principal Investigator that the proportion of HCL-32 positive subjects enrolled into the study could be greater than expected. As a consequence, a descriptive evaluation of the distribution of HCL-32 total score in 199 out of 202 subjects present in database on 20th of February 2012 was performed. The number of patients enrolled on 29th February 2012 was shown to be sufficient for detecting as statistically significant an absolute difference in the HCL-32 score of 2.1 with standard deviation of 6.31, α=0.05 and a power of almost 90%. For that reason on 14th March 2012 the enrolment was closed with a total of 446 patients were finally enrolled.

During the above mentioned evaluation no test for the primary comparison was performed.

Moreover, on the contrary of what specified in the "Statistical Analysis Plan" (version 2 – 21/09/2012), the logistic models were carried out without the factor 'psychiatric diagnosis' because all patients were classified as having a diagnosis of MDD.

Previous and current anti-depressive medication were described by Preferred Term and ATC codes (level two) of the WHO-DRL dictionary, version Q4-2010 instead of Q4-2009.

No other changes from what planned were made in the conduct of the analysis.

9.4 Population Analysis Sets

9.4.1 Definition of the target population

Twenty-nine centres, out of the 32 activated, enrolled a total of 446 patients. The first patient was enrolled the 19/05/2011 and the last patient the 14/03/2012.

Apart from one patient with missing diagnosis, all patients enrolled had a diagnosis of MDD according to DSM-IV TR.

Out of the 446 patients enrolled, 256 (57.40%) had a HCL-32 Total Score greater than or equal to 12 so belonging to the group with hypomanic symptoms,., 185 (41.48%) . had a HCL-32 Total Score lower than 12 belonging to the group without hypomanic symptoms, i.e

Overall, 5 patients (1.12%) were not Group Defined (Patients 1115, 2003, 2804, 4013, 4204) since their missing data did not allow to classify them as belonging to the Hypomanic or Not Hypomanic Group.

As emerged during the evaluation done in course of the study conduction, before re-estimation of the sample, the proportion of HCL-32 positive subjects enrolled was confirmed to be greater than expected (43.9%),

Overall 3 patients (0.67%) discontinued the study. Reasons for discontinuation are reported in the following Table 2.

Table 2: Patients disposition by group (Enrolled patients)

		Total Sample		Hypomanic Group		Not Hypomanic Group	
		N=446		N=256		N=185	
		N	%	N	%	N	%
Enrolled Patients		446	100.00	256	100.00	185	100.00
Discontinuers		3	0.67	-	-	2	1.08
Reason for discontinuation	**Age > 65 (Pt 4013)**	1	0.22	-	-	-	-
	Patient didn't want to continue the questionnaire (Pt 1120)	1	0.22	-	-	1	0.54
	Patient unable to remember good period of her life while was doing HCL32 (Pt 2511)	1	0.22	-	-	1	0.54

Further details about patients' disposition are shown in Tables 1.1-1 and 1.1-2 in the "Tables and Figures" document.

Overall, 4 patients (0.90%) were enrolled despite they had exclusion criteria confirmed (Exclusion criteria confirmed=Yes), as reported in the following Table 3.

Table 3: Listing of protocol violators (Enrolled patients)

Unique Subject Identifier	Date of Informed Consent	Inclusion criteria confirmed ?	Exclusion criteria confirmed ?	Group
2511	13SEP2011	Yes	Yes	Not Hypomanic Group
3021	27FEB2012	Yes	Yes	Not Hypomanic Group
3601	03OCT2011	Yes	Yes	Not Hypomanic Group
4117	13DEC2011	Yes	Yes	Not Hypomanic Group

9.5 Statistical Analysis Result

9.5.1 Dataset analysed

Out of the 446 patients enrolled, 441 patients (98.88%) were Group Defined, i.e. whose belonging to one group did not depend upon missing data. Out of these, 256 (58.05%) belonged to the group with hypomanic symptoms, 185 (41.95%) belonged to the group without hypomanic symptoms. Patients 1115, 2003, 2804, 4013, 4204 were not Group Defined. More specifically, Patient 4013 had no answer in HCL Questionnaire.

A total of 420 patients (94.17%) were Completer Patients, i.e. without missing data in the 32 items of HCL-32, 242 (57.62%) belonged to the group with hypomanic symptoms, 178 (42.38%) belonged to the group without hypomanic symptoms.

More details are shown in the following Tables 4 and 5.

Table 4: Analysis Population (Enrolled patients)

	Total Sample N=446		Hypomanic Group N=256		Not Hypomanic Group N=185	
	N	%	N	%	N	%
Enrolled Patients	446	100.00	256	100.00	185	100.00
Group Defined Patients	441	98.88	256	100.00	185	100.00
Completer Patients	420	94.17	242	94.53	178	96.22

Table 5: Hypomanic and Not Hypomanic Patients distribution

	Enrolled Patients N=446		Group Defined Patients N=441		Completer Patients N=420	
	N	%	N	%	N	%
Hypomanic	256	57.40	256	58.05	242	57.62
Not Hypomanic	185	41.48	185	41.95	178	42.38
Not Group Defined	5	1.12	-	-	-	-

9.5.2 Descriptive Analysis: demographic and baseline characteristics

In the total sample of enrolled patients, a mean age of 48.62±10.58 years, ranging from 21 to 72 years, was recorded. The maximum value of 72 years was recorded for Patient 4013 who discontinued the study. In the hypomanic group the mean age was 47.66±10.41 years with a range from 22 to 65 years. In the not hypomanic group the mean age was 49.84±10.67 years with a range from 21 to 66 years. The difference between the two groups was statistically significant: not hypomanic patients were older than hypomanic patients (Wilcoxon Rank-Sum Test p-value=0.0196).

As regard gender, a higher prevalence of females was observed. Among enrolled patients, 141 (31.61%) were males, 305 (68.39%) were females. The distribution was homogeneous in the hypomanic and not hypomanic group. In the hypomanic group there were 80 (31.25%) males and 176 (68.75%) females; in the not hypomanic group 59 (31.89%) patients were males and 126 (68.11%) were females.

Summary statistics of demographic characteristics are provided in the following Table 6 and 7.

Table 6: Gender (Enrolled patients)

		Total Sample		Hypomanic Group		Not Hypomanic Group	
		N=446		N=256		N=185	
		N	%	N	%	N	%
Gender	**Male**	141	31.61	80	31.25	59	31.89
	Female	305	68.39	176	68.75	126	68.11

Table 7: Age (Enrolled patients)

		Total Sample	Hypomanic Group	Not Hypomanic Group
		N=446	N=256	N=185
Age (years)	**N**	446	256	185
	Mean	48.62	47.66	49.84
	Std. Dev	10.58	10.41	10.67
	Median	50.00	49.00	52.00
	Min	21	22	21
	Max	72	65	66

In the enrolled population, the more represented professional categories were 'Employed' (32.06%), 'Homemaker' (30.94%), 'Unemployed' (17.49%) and 'Retired' (10.54%).

As shown in the Table 8, the distribution was not homogeneous between hypomanic and not hypomanic patients (Fisher's Exact Test p-value=0.0216).

Table 8: Professional Status (Enrolled patients)

		Total Sample N=446		Hypomanic Group N=256		Not Hypomanic Group N=185	
		N	%	N	%	N	%
Professional status	**Missing**	1	0.22	-	-	-	-
	Employed or has own business	143	32.06	93	36.33	50	27.03
	Unemployed	78	17.49	45	17.58	32	17.30
	Homemaker	138	30.94	71	27.73	64	34.59
	Retired	47	10.54	22	8.59	25	13.51
	Student	22	4.93	10	3.91	12	6.49
	Sick leave	9	2.02	8	3.13	1	0.54
	Maternity leave or disability pension	8	1.79	7	2.73	1	0.54

As reported in the following Table 9, enrolled patients were mainly married (58.97%). Lower prevalence was reported for the family categories 'Never married' (22.87%), 'Separated' (8.52%), 'Divorced' (5.16%) and 'Widowed' (4.26%). No inhomogeneity between hypomanic and not hypomanic patients was detected.

Table 9: Family Status (Enrolled patients)

		Total Sample N=446		Hypomanic Group N=256		Not Hypomanic Group N=185	
		N	%	N	%	N	%
Family status	**Missing**	1	0.22	-	-	-	-
	Never married	102	22.87	62	24.22	39	21.08
	Married	263	58.97	151	58.98	110	59.46
	Separated	38	8.52	23	8.98	14	7.57
	Divorced	23	5.16	10	3.91	13	7.03
	Widowed	19	4.26	10	3.91	9	4.86

Further details about patients demographics characteristics, professional and family status are reported in Tables 1.4-1 and 1.4-2 in the “Tables and Figures” document.

In the enrolled population, only Patient 4013 had missing information about diagnosis, while for all other patients a diagnosis of MDD was confirmed.

The onset of the current episode was in mean 7.85±19.24 months before the study visit. A great variability was detected, as revealed by the wide range from 0 to 312.43 months. No statistically significant difference between hypomanic and not hypomanic group was detected. In the hypomanic group the onset of the current episode was in mean 6.27±7.52 months before the study visit, 3.87 in median and ranging from 0 to 48.82, while in the not hypomanic group a mean of 10.12±28.36 months, 3.61 in median, elapsed, with an average influenced by a high maximum value of 312.43 months.

Among the enrolled patients, 3.58±13.50 episodes in average occurred in the year prior to the study visit, ranging from 0 to 200. A statistically significant difference was detected between hypomanic and not hypomanic group. The Wilcoxon Rank-Sum test detected a statistically significant difference in the ranked values, with a p-value=0.0245, suggesting a higher number of episodes in the hypomanic group (Mean Rank Score in Hypomanic Group= 231.34 vs. 205.42 in the Not Hypomanic Group). The non-normal distribution of the data made difficult to compare the summary statistics of the two groups, in particular the mean values. In the hypomanic group a mean of 3.30±10.98 was observed, ranging from 0 to 150, with a median of 2.0, while in the not hypomanic group the mean was 4.02±16.51 with a range from 0 to 200 and a median of 1.0.

Further details about time from the onset of the current episode and number of previous episodes in the last year are reported in the following Tables 10 and 11 and in Table 1.4-3 in the “Tables and Figures” document.

Table 10: Time from the onset of the current episode (Enrolled patients)

		Total Sample N=446	Hypomanic Group N=256	Not Hypomanic Group N=185
Elapsed months from the onset of the current episode	**N**	444	255	185
	Mean	7.85	6.27	10.12
	Std. Dev	19.24	7.52	28.36
	Median	3.79	3.87	3.61
	Min	0.00	0.00	0.00
	Max	312.43	48.82	312.43

Table 11: Number of previous episodes in the last year (Enrolled patients)

		Total Sample N=446	Hypomanic Group N=256	Not Hypomanic Group N=185
Number of previous episodes in the last year	**N**	444	256	184
	Mean	3.58	3.30	4.02
	Std. Dev	13.50	10.98	16.51
	Median	1.00	2.00	1.00
	Min	0	0	0
	Max	200	150	200

In the enrolled population, 97 patients (21.75%) had at least one relevant disease/pathology. A higher prevalence was recorded in the hypomanic group, with 66 patients (25.78%) presenting at least one relevant disease compared to 31 patients (16.76%) in the Not Hypomanic Group. The difference was statistically significant (Chi-Square p-value=0.0240).

The most reported diseases among enrolled patients were hypertension, presented in 25 patients (5.61%), 17 (6.64%) in the hypomanic group and 8 (4.32%) in the not hypomanic group; hypothyroidism, present in 13 patients (2.91%), 8 (3.13%) in the hypomanic group and 5 (2.70%) in the not hypomanic group; diabetes mellitus, presented in 10 patients (2.24%), 6 (2.34%) in the hypomanic group and 4 (2.16%) in the not hypomanic group.

Details of other diseases observed are reported in the Table 1.4-4 in the 'Tables and Figures' document.

In the enrolled sample a total of 437 (97.98%) reported at least one previous medication, 254 (99.22%) in the hypomanic group, 179 (96.76%) in the not hypomanic group.

The most reported previous treatments among enrolled patients were escitalopram oxalate reported in 75 (16.82%) patients, 38 (14.84%) in the hypomanic group, 37 (20.00%) in the not hypomanic group; duloxetine hydrochloride reported in 51 (11.43%) patients, 30 (11.72%) in the hypomanic group, 21 (11.35%) in the not hypomanic group; venlafaxine hydrochloride reported in 51 (11.43%) patients, 30 (11.72%) in the hypomanic group, 20 (10.81%) in the not hypomanic group; paroxetine hydrochloride reported in 48 (10.76%) patients, 22 (8.59%) in the hypomanic group, 26 (14.05%) in the not hypomanic group; bupropion hydrochloride reported in 26 (5.83%) patients, 18 (7.03%) in the hypomanic group, 7 (3.78%) in the not hypomanic group; sertraline hydrochloride reported in 23 (5.16%) patients, 13 (5.08%) in the hypomanic group, 9 (4.86%) in the not hypomanic group.

Details of other previous medications observed are reported in the Table 1.4-5 in the 'Tables and Figures' document.

In the enrolled sample a total of 443 (99.33%) reported at least one current medication, 256 (100.00%) in the hypomanic group, 183 (98.92%) in the not hypomanic group.

The most reported current medications among enrolled patients were duloxetine hydrochloride reported in 86 (19.28%) patients, 48 (18.75%) in the hypomanic group, 36 (19.46%) in the not hypomanic group; escitalopram oxalate reported in 86 (19.28%) patients, 46 (17.97%) in the hypomanic group, 40 (21.62%) in the not hypomanic group; venlafaxine hydrochloride reported in 75 (16.82%) patients, 47 (18.36%) in the hypomanic group, 27 (14.59%) in the not hypomanic group; paroxetine hydrochloride reported in 40 (8.97%) patients, 23 (8.98%) in the hypomanic group, 16 (8.65%) in the not hypomanic group; bupropion hydrochloride reported in 37 (8.30%) patients, 26 (10.16%) in the hypomanic group, 11 (5.95%) in the not hypomanic group; sertraline hydrochloride reported in 25 (5.61%) patients, 15 (5.86%) in the hypomanic group, 10 (5.41%) in the not hypomanic group.

Details of current antidepressive medications are reported in the following Table 12 and in the Table 1.4-6 in the 'Tables and Figures' document.

Table 12: Current Antidepressive Medication (Enrolled patients)

			Total Sample		Hypomanic Group		Not Hypomanic Group	
			N=446		N=256		N=185	
			N	%	N	%	N	%
	ATC Code - Level 2	Preferred Term						
N. of patients with at least one medication			443	99.33	256	100.00	183	98.92
	Antiepileptics	Carbamazepine	1	0.22	-	-	1	0.54
		Lamotrigine	1	0.22	-	-	1	0.54
		Levetiracetam	1	0.22	-	-	1	0.54
		Pregabalin	1	0.22	-	-	1	0.54
	Psychoanaleptics	Ademetionine	2	0.45	1	0.39	1	0.54
		Agomelatine	18	4.04	6	2.34	12	6.49
		Amitriptyline hydrochloride	12	2.69	6	2.34	6	3.24
		Bupropion hydrochloride	37	8.30	26	10.16	11	5.95
		Citalopram	3	0.67	3	1.17	-	-
		Citalopram hydrobromide	7	1.57	3	1.17	4	2.16
		Citalopram hydrochloride	8	1.79	6	2.34	2	1.08
		Clomipramine hydrochloride	8	1.79	6	2.34	2	1.08
		Duloxetine hydrochloride	86	19.28	48	18.75	36	19.46
		Escitalopram oxalate	86	19.28	46	17.97	40	21.62
		Fluoxetine hydrochloride	6	1.35	5	1.95	1	0.54
		Fluvoxamine maleate	4	0.90	3	1.17	1	0.54
		Mirtazapine	16	3.59	9	3.52	7	3.78
		Paroxetine hydrochloride	40	8.97	23	8.98	16	8.65
		Paroxetine mesilate	17	3.81	9	3.52	8	4.32
		Reboxetine mesilate	2	0.45	1	0.39	1	0.54
		Sertraline hydrochloride	25	5.61	15	5.86	10	5.41
		Trazodone hydrochloride	8	1.79	4	1.56	4	2.16
		Venlafaxine hydrochloride	75	16.82	47	18.36	27	14.59

	Psycholeptics	Alprazolam	7	1.57	1	0.39	6	3.24
		Amisulpride	5	1.12	3	1.17	2	1.08
		Aripiprazole	6	1.35	3	1.17	3	1.62
		Delorazepam	1	0.22	1	0.39	-	-
		Lithium carbonate	1	0.22	-	-	1	0.54
		Olanzapine	1	0.22	1	0.39	-	-
		Paliperidone	1	0.22	-	-	1	0.54
		Quetiapine fumarate	8	1.79	5	1.95	3	1.62
		Risperidone	6	1.35	4	1.56	2	1.08
		Triazolam	1	0.22	1	0.39	-	-
		Zolpidem tartrate	1	0.22	-	-	1	0.54
	Unspecified herbal and traditional medicine	Hypericum perforatum	1	0.22	-	-	1	0.54

In the enrolled population, 354 (79.37%) patients had a treatment switch in the last year. The distribution was quite homogeneous in the two groups: a treatment switch in the last year was reported in 201 (78.52%) patients in the Hypomanic group and in 149 (80.54%) patients in not hypomanic group, as reported in the following Table 13.

More details have been reported in Table 1.4-7 in ‘Tables and Figures’ document.

Table 13: Treatment Switch in the Last Year (Enrolled patients)

		Total Sample		**Hypomanic Group**		**Not Hypomanic Group**	
		N=446		**N=256**		**N=185**	
		N	**%**	**N**	**%**	**N**	**%**
Treatment Switch in the Last Year	**No**	92	20.63	55	21.48	36	19.46
	Yes	354	79.37	201	78.52	149	80.54

9.5.1 Efficacy Results

Primary Objective

HCL-32 total score was calculated as the sum of the positive answers in the 32 items of the HCL-32 questionnaire.

In the primary efficacy population, i.e. the Completer patients, the mean HCL-32 total score was 12.95±6.23, ranging from 0 to 29. In the hypomanic group the mean was 17.34±3.87 with a minimum and maximum value of 12 and 29, while in the not hypomanic group the mean total score was 6.99±3.05, with minimum and maximum value respectively of 0 and 11. The difference in means was 10.35 with 95% CI of 9.69-11.01 (computed with Satterthwaite method for unequal variance groups). The null hypothesis of equality of the means was refused with a high level of statistical significance (p-value <0.0001 at T Test). Hypomanic patients had a HCL-32 total score significantly higher than not hypomanic patients.

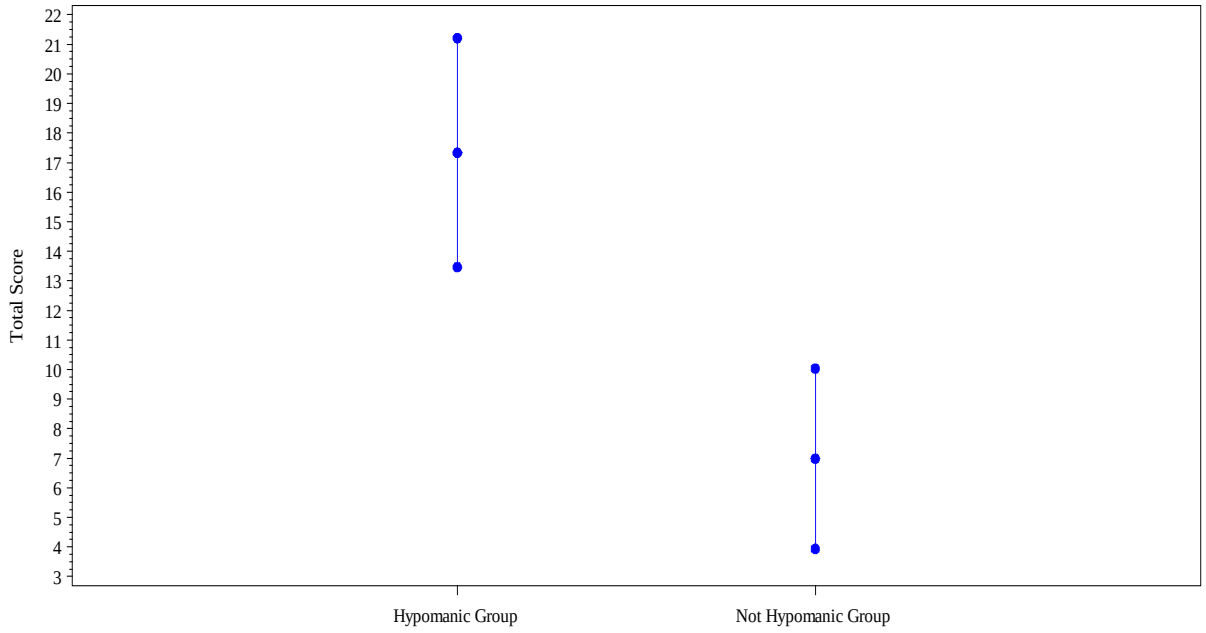
More details have been reported in the following Table 14 and in the Tables 2.2-1 and 2.2-2 in the 'Tables and Figures' document.

Table 14: HCL-32 Total Score - Descriptive Statistics (Completer Patients)

		Total Sample N=420	Hypomanic Group N=242	Not Hypomanic Group N=178
HCL-32 Total Score	**N**	420	242	178
	Mean	12.95	17.34	6.99
	Std. Dev	6.23	3.87	3.05
	Median	13.00	17.00	7.00
	Min	0	12	0
	Max	29	29	11

The following Figure 2 provided a graphical representation of the results.

Figure 2: HCL-32 Total Score (Completer Patients)



Mean values +/- Standard Deviations are reported

In the completers population results were presented also for two sub-scores each addressing one specific variant of hypomanic behaviour: “active/elated hypomania” and “irritable/risk-taking hypomania”computed as the sum of positive answers of items specified in 9.2.2 section

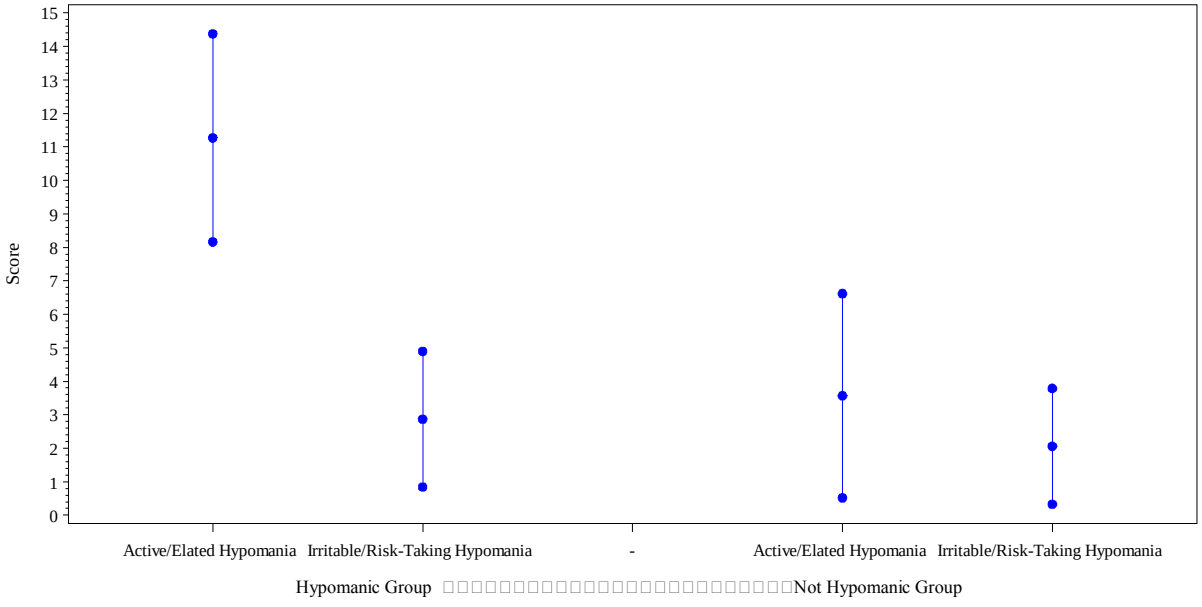
In the population of completers, active/elated hypomania score was in mean 8.01±4.90 ranging 0 to 16. An high difference among the two group was detected: the mean was 11.27±3.11 in the hypomanic group, 3.57±3.05 in the not hypomanic group. The irritable/risk-taking hypomania score was instead more homogeneous in the two groups: it was reported with mean 2.53±1.95 overall in the completers population, ranging from 0 to 8, 2.87±2.03 in the hypomanic group, 2.06±1.73 in the not hypomanic group.

Descriptive statistics and graphical representation are reported in the following Table 15 and Figure 3.

Table 15: HCL-32 Sub-Scores - Descriptive Statistics (Completer Patients)

		Total Sample N=420	Hypomanic Group N=242	Not Hypomanic Group N=178
Active/Elated Hypomania Score	**N**	420	242	178
	Mean	8.01	11.27	3.57
	Std. Dev	4.90	3.11	3.05
	Median	8.00	12.00	3.00
	Min	0	3	0
	Max	16	16	11
Irritable/Risk-Taking Hypomania Score	**N**	420	242	178
	Mean	2.53	2.87	2.06
	Std. Dev	1.95	2.03	1.73
	Median	2.00	3.00	2.00
	Min	0	0	0
	Max	8	8	7

Figure 3: HCL-32 Sub-Scores (Completer Patients)



Mean values +/- Standard Deviations are reported

Overall, when filling in the question asking the feeling of today compared to the usual state, Completer patients felt mainly 'Neither better nor worse than usual' (21.67%) or 'A little worse than usual' (21.19%) or 'Worse than usual' (20.95%). Lower frequencies were reported for conditions better than usual and for condition much better or worse than usual. In particular 15.71% of patients felt 'A little better than usual', 8.81% 'Better than usual', 7.62% 'Much worse than usual' and 3.33% 'Much better than usual'.

In the hypomanic group patients lower frequencies were reported for the worse than usual conditions compared to the not hypomanic group patients: 'Much worse than usual' was reported in 5.79% in the hypomanic group vs. 10.11% in the not hypomanic group, 'Worse than usual' in 19.83% vs. 22.47%, 'A little worse than usual' in 18.60% vs. 24.72%. On the contrary, higher frequencies for the better than usual conditions were reported: 'a little better than usual' 16.12% vs. 15.17%, 'better than usual' 11.98% vs. 4.49%, 'much better than usual' 5.37% vs. 0.56%.

Overall among Completer patients, the aspects reported to be more influenced during high periods were inclination to be more self-confident (62.86%), more optimistic (61.19%), more energetic and active (61.19%) and to talk more (60.24%)

On the contrary, more than 80% of Completer patients during their 'high' periods described themselves not as more likely to drink (86.90%), nor to drive faster (86.19%), nor to act in a much risky manner (82.14%). High periods were not associated in more than three quarters of the Completer patients also to a predisposition in spending too much money (78.57%), nor to taking more drugs (77.86%), nor to choosing for more colourful clothes or make-up (77.14%), nor to smoking more cigarettes (75.95%), nor to getting into more quarrels (75.71%).

Among hypomanic Completer patients, the aspects reported to be more influenced during high periods were inclination to be more self-confident (83.47%), to talk more (82.64%), to be more energetic and active (82.23%) and more optimistic (81.40%). In the not hypomanic Completer patients more reported inclinations during high periods were being more impatient/irritable (53.37%), more easily distracted (43,82%), exhausting/irritating for others (37,64%) and having thoughts jumping from topic to topic (37,64%).

The aspects to be more differently influenced in hypomanic group patients vs. not hypomanic patients were the inclinations to be more sociable (80.58% vs. 26.40% of patients in hypomanic group vs. not hypomanic group), to talk more (82.64% vs. 29.78%), to meet more people (71.90% vs. 19.10%), to be physically more active (69.83% vs. 17.42%), to be more creative (76.86% vs. 24.72%), to make more jokes or puns (64.88% vs. 12.92%), to do things more quickly/easy (67.36% vs. 16.29%).

Overall 66.19% of Completer patients felt to be described by their answers to the questionnaire 'Sometimes'. This percentage was lower in the hypomanic group: 58.26% vs. 76.97% in the not hypomanic group.

The 76.76% of remaining Completer patients declared to be represented by their answers to the questionnaire for most of the times. Among those, a mean of 2.44±5.37 different "highs" were recorded in the past twelve months and 15.11±21.89 in their entire life. In the hypomanic group

more episodes were recorded than in the not hypomanic group: 2.61±5.80 vs. 1.97±3.99 episodes in the past twelve months and 17.32±24.56 vs. 9.24±10.50 in the entire life. The length on the average of the "highs" was mainly longer than a week, as reported for 44.09% of Completers patient overall, 44.57% in the hypomanic group and 42.86% in the not hypomanic group. The longest high was reported to be of 167.17±317.39 days. A great variability was detected both in the hypomanic group with a mean of 183.28±358.77 days and in the not hypomanic group with a mean of 130.33±194.90 days.

Overall the high periods were mainly perceived with a positive impact on family life (42.52%), on social life (48.82%), on work (45.67%) and positively commented by people (40.94%). The impact was greater in the hypomanic group than in not hypomanic group.

Compared to other people level of activity, energy and mood was reported to be generally lower overall in 273 (67.41%) Completers patient, 146 (62.66%) in the hypomanic group, 127 (73.84%) in the not hypomanic group. In 156 (38.52%) patients of the completers population, 76 (32.62%) in the hypomanic group, 80 (46.51%) in the not hypomanic group, the level was reported to be rather stable and even.

No significant difference in the enrolled patients population had to be highlighted.

Further details about the distribution of the answers to the single items of the HCL-32 questionnaire have been reported in the Table 2.2-1 and 2.2-4 of the 'Tables and Figures' document.

Sensitivity analysis

A sensitivity analysis was performed excluding only patients with undefined group due to missing data for the 32 items of HCL-32 questionnaire used to compute the total score.

For the Best Scenario missing values to any of the 32 items of HCL-32 questionnaire used to compute the total score were replaced with affirmative answers.

The resulting HCL-32 total score was in mean 13.03±6.24, ranging from 0 to 29. In the hypomanic group the mean was 17.41±3.84 with a minimum and maximum value of 12 and 29, while in the not hypomanic group the mean total score was 6.98±3.03, with a minimum and maximum value respectively of 0 and 11. The difference in means was 10.43 with 95%CI of 9.78-11.07 (computed with Satterthwaite method for unequal variance groups). This assumption about missing data do not change results: hypomanic patients had a higher HCL-32 total than not hypomanic patients with a high level of statistical significance (p-value <0.0001 at T Test).

More details have been reported in the following Table 16 and in the Tables 2.3-1 and 2.3-2 in the 'Tables and Figures' document.

Table 16: HCL-32 Total Score - Descriptive Statistics (Group Defined Patients - Best Scenario)

		Total Sample N=441	Hypomanic Group N=256	Not Hypomanic Group N=185
HCL-32 Total Score	**N**	441	256	185
	Mean	13.03	17.41	6.98
	Std. Dev	6.24	3.84	3.03
	Median	13.00	17.00	7.00
	Min	0	12	0
	Max	29	29	11

In the Worst Scenario negative answers were replaced to missing values in any of the 32 items of HCL-32 questionnaire used to compute the total score.

Any significant influence on the results was observed. The resulting mean HCL-32 total score was 12.98±6.23, ranging from 0 to 29. In the hypomanic group the mean was 17.34±3.83 with a minimum and maximum value of 12 and 29, while in the not hypomanic group the mean total score was 6.94±3.04, ranging from 0 to 11. The difference in means was 10.40 with 95% CI of 9.75-11.04 (computed with Satterthwaite method for unequal variance groups). The HCL-32 total score in hypomanic patients was statistically significant higher than in not hypomanic patients (p-value for T Test <0.0001).

Results have been reported in the following Table 17 and in the Tables 2.4-1 and 2.4-2 in the 'Tables and Figures' document.

Table 17: HCL-32 Total Score - Descriptive Statistics (Group Defined Patients - Worst Scenario)

		Total Sample N=441	Hypomanic Group N=256	Not Hypomanic Group N=185
HCL-32 Total Score	**N**	441	256	185
	Mean	12.98	17.34	6.94
	Std. Dev	6.23	3.83	3.04
	Median	13.00	17.00	7.00
	Min	0	12	0
	Max	29	29	11

A Prevalence Approach was also applied: missing values in each Group Defined patient were replaced by his/her proportion of positive answers in the filled items.

Also in this case only minimal influence on the results were observed. Overall, HCL-32 total score was in mean 13.00±6.24, ranging from 0 to 29. In the hypomanic group the mean was 17.37±3.84 with a minimum and maximum value of 12 and 29, while in the not hypomanic group the mean total score was 6.95±3.04, ranging from 0 to 11. The difference in means was 10.43 with 95%CI of 9.78-11.07 (computed with Satterthwaite method for unequal variance groups). Also in this scenario hypomanic patients had a higher HCL-32 total score than not hypomanic patients, with a high level of statistical significance (p-value for T Test <0.0001).

More details have been reported in the following Table 18 and in the Tables 2.5-1 and 2.5-2 in the 'Tables and Figures' document.

Table 18: HCL-32 Total Score - Descriptive Statistics (Group Defined Patients - Prevalence Approach)

		Total Sample N=441	Hypomanic Group N=256	Not Hypomanic Group N=185
HCL-32 Total Score	**N**	441	256	185
	Mean	13.00	17.37	6.95
	Std. Dev	6.24	3.84	3.04
	Median	13.00	17.00	7.00
	Min	0	12	0
	Max	29	29	11

To illustrate the robustness of the conclusions, a sensitivity analysis was performed for the primary efficacy variable, also on all enrolled patients.

As previously, in the Best Scenario missing values were replaced with positive answers, in the Worst Scenario with negative ones and in the Prevalence Approach with the mean proportion of positive answers. Among all enrolled patients, this replacement made changes in the distribution of the patients in the hypomanic and not hypomanic groups, affecting the belonging to one group or another of the patients not Group Defined. In these analyses one patient without any answers to the questionnaire was excluded. Results did not significantly change than ones in the primary analysis.

In the Best Scenario, overall HCL-32 total score was in mean 13.09±6.28, with a minimum and maximum values respectively of 0 and 32. Among the 260 patients in the hypomanic group, the mean of HCL-32 total score was 17.43±3.93, ranging from 12 to 32, while in the not hypomanic patients the mean of HCL-32 total score was 6.98±3.03 with a minimum and maximum values respectively of 0 and 11. The difference in means was 10.45 with 95% CI of 9.80-11.10 (computed with Satterthwaite method for unequal variance groups significantly different from 0 (p-value for T Test <0.0001).

More details are reported in the following Table 19 and in the Tables 2.6-1, 2.6-2 and 2.6-3 in the ‘Tables and Figures’ document.

Table 19: HCL-32 Total Score - Descriptive Statistics (Enrolled Patients - Best Scenario)

		Total Sample N=445	Hypomanic Group N=260	Not Hypomanic Group N=185
HCL-32 Total Score	**N**	445	260	185
	Mean	13.09	17.43	6.98
	Std. Dev	6.28	3.93	3.03
	Median	13.00	17.00	7.00
	Min	0	12	0
	Max	32	32	11

In the Worst Scenario, the HCL-32 total score was in mean 12.93±6.22, ranging from 0 to 29. In the hypomanic group the mean was 17.34±3.83 with a minimum and maximum value of 12 and 29, while in the not hypomanic group the total score was in mean 6.96±3.03, ranging from 0 to 11. The difference in means was 10.37 with 95%CI of 9.73-11.01 (computed with Satterthwaite Method for unequal variance groups). Also with this approach the hypomanic patients had a HCL-32 total score higher than not hypomanic patients, with a high level of statistical significance (p-value for T Test <0.0001).

Descriptive statistics are summarized in the following Table 20 and in the Tables 2.7-1, 2.7-2 and 2.7-3 in the 'Tables and Figures' document.

Table 20: HCL-32 Total Score - Descriptive Statistics (Enrolled Patients - Worst Scenario)

		Total Sample N=445	Hypomanic Group N=256	Not Hypomanic Group N=189
HCL-32 Total Score	**N**	445	256	189
	Mean	12.93	17.34	6.96
	Std. Dev	6.22	3.83	3.03
	Median	13.00	17.00	7.00
	Min	0	12	0
	Max	29	29	11

In the Prevalence approach, the resulting HCL-32 total score was in mean 12.97±6.22, ranging from 0 to 29. In the hypomanic group the mean was 17.37±3.84 with a minimum and maximum value of 12 and 29, while in the not hypomanic group the mean total score was 7.01±3.05, with a minimum and maximum value respectively of 0 and 12. The difference in means was 10.36 with 95%CI of 9.72-11.00 (computed with Satterthwaite method for unequal variance groups). This assumption about missing data did not change results: hypomanic patients had a higher HCL-32 total score than not hypomanic patients with a high level of statistical significance (p-value for T Test <0.0001).

More details have been reported in the following Table 21 and in the Tables 2.8-1, 2.8-2 and 2.8-3 in the 'Tables and Figures' document.

Table 21: HCL-32 Total Score - Descriptive Statistics (Enrolled Patients – Prevalence Approach)

		Total Sample	Hypomanic Group	Not Hypomanic Group
		N=445	N=256	N=189
HCL-32 Total Score	**N**	445	256	189
	Mean	12.97	17.37	7.01
	Std. Dev	6.22	3.84	3.05
	Median	13.00	17.00	7.00
	Min	0	12	0
	Max	29	29	12

Secondary efficacy analysis

An explorative multivariate analysis was provided in order to investigate the effect of explicative factors on hypomanic condition status, identified by HCL-32 total score.

A logistic regression model was fitted in order to examine among the Completer patients the relation of belonging to the group of hypomanic patients rather than to the not hypomanic group with the factors age, gender, family status, professional status, time elapsed from the onset of the current episode, number of previous episodes in the last year, relevant disease/pathology that could interfere with this pathology/treatment and treatment switch in the year previous to the enrolment. In table 22 below the Odds Ratio with 95% Confidence Limits are reported for each factor considered. Age was significantly associated with the hypomanic condition (p-value=0.0028): one year age increment made a 4% decrease in the probability of belonging to the

group of hypomanic patients against the probability of belonging to the not hypomanic group. The Odds Ratio was 0.96 with 95%CI of 0.94-0.99.

Gender appeared not to influence the hypomanic status (p-value=0.6282): the Odds Ratio for females vs. males was 1.13 not significant with 95%CI of 0.68-1.88. though in the analyzed sample being female meant to have a 13% higher probability of belonging to the hypomanic group rather than to the not hypomanic group.

Professional status was significantly associated with hypomanic condition (p-value=0.0227). In particular, considering employees as reference category, students had a significantly lower (p-value=0.0144) probability of belonging to the group of hypomanic patients against the probability of not belonging, with an Odds Ratio of 0.26 with 95%CI of 0.09-0.76. Not statistically significant were the comparisons for the other categories. Family status did not significantly affect the hypomanic status (p-value=0.5493). Elapsed time from the onset of the current episode was significantly associated with the hypomanic condition (p-value=0.0167): with the increase of one month a 2% decrease in the probability of belonging to the group of hypomanic patients against the probability of belonging to the not hypomanic group. The Odds Ratio was 0.98 with 95% CI of 0.959-0.996.

Number of previous episodes in the last year and having a treatment switch in the last year did not influence the probability of belonging to one group against the other (p-value=0.5080 and p-value=0.5660, respectively).

The absence of concomitant diseases or pathologies that could interfere on the depressive disorders was associated to the not hypomanic condition (p-value=0.0115): the probability of belonging to hypomanic group vs. the not hypomanic group was 50% lower in patients without concomitant diseases or pathologies. The Odds Ratio was 0.50 with 95% CI of 0.29-0.86.

As regards the model fit statistics, the model explained only 10.16% of the variability of the dependent variable. However, the test of goodness-of-fit is not significant (p-value=0.9038), meaning that the null hypothesis that there was no difference between the observed and predicted values of the response variable could not be refused.

No relevant difference in the results arose in the model build up with a step-wise selection of the variables. The factors included were those whose significance was proved also in the full model. No particular changes in the estimates of Odds Ratio were to be underlined.

Table 22: HCL-32 Hypomanic Conditions Status Multivariate Logistic Model (Completer patients)-

			Odds Ratio Estimates		
				95% CI	
			Estimate	Lower	Upper
Probability of Hypomanic Group vs Not Hypomanic Group	**Age**	**1 year increment**	0.96	0.94	0.99
	Sex	**Male**	Ref	Ref	Ref
		Female	1.13	0.68	1.88
	Professional Status	**Employed or has own business**	Ref	Ref	Ref
		Student	0.26	0.09	0.76
		Homemaker	0.58	0.33	1.01
		Retired	0.61	0.28	1.32
		Unemployed	0.83	0.45	1.52
		Sick leave	7.00	0.78	62.70
		Maternity leave or disability pension	43.25	0.08	23199.87
	Family Status	**Married**	Ref	Ref	Ref
		Divorced	0.43	0.17	1.11
		Never married	0.89	0.48	1.65
		Separated	0.89	0.41	1.94
		Widowed	1.00	0.37	2.73
	Time elapsed from the onset of the current episode	**1 month increment**	0.98	0.96	1.00
	Number of previous episodes in the last year	**1 episode increment**	0.99	0.98	1.01
	Any relevant disease/pathology that could interfere	**Yes**	Ref	Ref	Ref
		No	0.50	0.29	0.86
	Treatment switch	**Yes**	Ref	Ref	Ref
		No	1.17	0.69	1.99

9.5.2 Statistical/analytical issues

When considering the Enrolled patients population, only patients whose belonging to one group did not depend upon missing data, i.e. Group Defined patients, have been classified in the Hypomanic or Not Hypomanic Group. Patients 1115, 2003, 2804, 4013, 4204 were not Group Defined. Patient 4013 had no answer in HCL Questionnaire and was excluded also from populations for sensitivity analysis.

As reported in section 9.2.1, missing data in day and/or month of onset of the current episode were imputed according to the assumptions day=15 and/or month=6. Patient 2509 and 4013 had missing date of onset of the current episode.

Likewise, in the analysis of treatment Switch in the Year previous to the study, for missing data in day and/or month of start/end of treatment the assumptions day=15 and/or month=6 were made. Patients 1703, 3806, 3807, 3811, 3812, 4127 had only one treatment reported and they were considered having no treatment switch.

In the analysis of medical history a patient could report more than one disease/pathology. In the tables of Previous and Current Antidepressive Medication a patient could report more than one therapy. For Limbitryl, Mutabon Forte and Mutabon Mite the preferred term was replaced with the low level term, since it should indicate the active substance rather than a brand name.

10. SAFETY

Not applicable.

11. ETHICS

The protocol was approved by the Independent Ethics Committees (IECs) of all study centres.

11.1 Ethical conduct of study

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonisation (ICH) / Good Clinical Practice (GCP) and applicable regulatory requirements and the AstraZeneca policy on Bioethics.

11.2 Subject information and consent

Signed informed consent was obtained from all patients prior to enrolment and prior to apply any study procedure.

This clinical study was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with the exceptions applicable to observational studies, with applicable local regulations (including European Directive

2001/83/EC and US Code of Federal Regulations Part 21), and with the ethical principles laid down in the Declaration of Helsinki.

12. CONCLUSION(S)

Hypomania is a lowered state of mania that does little to impair function or decrease quality of life. Though the elevated mood and energy level typical of hypomania could be seen as a benefit, mania itself generally has many undesirable consequences including suicidal tendencies.

Misdiagnosis or inaccurate diagnosis of hypomania is very important for patients who are treated with antidepressants (11). They are ineffective in treating acute bipolar depression, preventing relapse and can cause several risks when given to bipolar patients including rapid cycling and a higher rate of non-lethal suicidal behavior. Relapse can also be related to treatment with antidepressants. This is less likely to occur if a mood stabilizer is combined with an antidepressant, rather than an antidepressant being used alone (8).

Misdiagnosis can prevent the patients with bipolar disorder from receiving medication like lithium useful to treat the disorder. So it is critical to identify bipolar patients so appropriate treatment can be given.

The patients included in the present study were treatment-resistant, defined as non-responsive to at least 2 antidepressants given in an adequate dose for a sufficient duration (following the specific SmPC) and with last antidepressant treatment on-going.

The overall mean of HCL-32 total score is shown to be 12.95, a bit higher in comparison with the total score of 11.9 in treatment-resistant subgroup in the large Polish study by Dudek (10); even if it is always hard to compare data of a current study with historical data this result is suggesting there are some differences in the patients enrolled in the two studies like inclusion/exclusion criteria and clinical care setting.

In our completer patients population, 242 out of 420 were HCL-32 positive, i.e. had a HCL-32 total score greater than or equal to 12, giving a prevalence of 57.62% hypomanic subjects. This prevalence is a bit higher than that shown in the above study, where in the subgroup of treatment-resistant patients HCL-32 positive were 43.9%. One reason of this discrepancy is that the cut-off adopted in the Polish study was 14 or more positive answers, while in our study the cut-off of 12 has been adopted; as consequence about 10% more subjects were classified as positive being their total score between 12 and 13.

In the hypomanic group the HCL-32 total score mean was 17.34, while in the not hypomanic group it was 6.99. The difference in means has a high level of statistical significance, so confirming the reliability of the HCL-32 as sensitive instrument to discriminate bipolarity as possible cause of drug resistance from other causes in depressive patients.

In particular, also the active/elated hypomania score was 8.01 confirming a high difference in comparison with not hypomanic group.

All the approaches applied to the sensitivity analyses, with the different imputations to missing data in the best and worst scenarios as well as in prevalence scenario, had only minimal influence on the results as regards the capacity of HCL-32 questionnaire to discriminate between hypomanic and non-hypomanic patients so providing reasonable assurance that the overall study conclusions are quite robust.

In comparison with not hypomanic patients, the hypomanic group is younger, has a lower proportion of students and homemakers, their time elapsed from the onset of current episode was shorter, while the number of previous episodes was higher as well as the presence of concomitant diseases.

Considering also the single items of HCL-32 the hypomanic group was quite well characterized: the aspects to be more influenced were the inclination to be more sociable, to talk more, to meet more people, to be physically more active, to be more creative, to make more jokes or puns and to do things more quickly/easy.

The logistic regression model applied confirmed that belonging to the group of hypomanic patients was significantly associated with age, professional status, elapsed time from the onset of the current episode and presence of concomitant diseases or pathologies that could interfere on the depressive disorders.

In conclusion our study results confirmed the high sensitivity of HCL-32, a simple and easy to use instrument in detecting hypomanic symptoms in treatment-resistant depressive patients.

13. DATE OF THE REPORT

28/01/2013

14. REFERENCES

1. Angst J, Adolfsson R, Benazzi F, et al. The HCL-32: towards a self-assessment tool for hypomanic symptoms in out-patients. JAD 2005; 88: 217-233.

2. Angst J. Do many patients with depression suffer from bipolar disorder? Can J Psychiatry 2006; 51: 3–5.

3. Judd LL, Paulus MJ, Schettler PJ, et al. Does incomplete recovery from first lifetime major depressive episode herald a chronic course of illness? Am J Psychiatry 2000; 157: 1501–1504.

4. Thase ME. Update on partial response in depression. J Clin Psychiatry 2009; 70 (suppl 6): 4-9.

5. Halpern JK, Glassman AH. Adequate tricyclic treatment: defining the tricyclic non-responder. In: Roose SP, Glassman AH (Eds.) Treatment Strategies for Refractory Depression. American Psychiatric Press, Washington, DC, 1990; pp. 11–32.

6. Roose SP. Methodological issues in the diagnosis, treatment and study of refractory depression. In: Roose SP, Glassman AH (Eds.) Treatment Strategies for Refractory Depression. American Psychiatric Press, Washington, DC, 1990; pp. 3–9.

7. Thase ME, Rush AJ. Treatment-resistant depression. In: Bloom, FE, Kupfer DJ (Eds.) Psychopharmacology: The fourth Generation of Progress. Raven Press, NY, 1995; pp. 1081–1097.

8. Van den Berg B., Penninx B.W.J.H., Zitman F.G., Nolen W.A. Manic symptoms in patients with depressive and/or anxiety disorders. Journal of Affect Disord 03/2010; 126(1-2):252-6. doi:10.1016/j.jad.2010.02.130

9 Carta MG, Hardoy MC, Cadeddu M, et al. The accuracy of the Italian version of the hypomania checklist (HCL-32) for the screening of bipolar disorders and comparison with the Mood Disorder Questionnaire (MDQ) in a clinical sample. Clin Pract Epidemiol Ment Health 2006; 1:8 doi:10.1186/1745-0179-1-8.

10. Dudek D, Rybakowski JK, Siwek M, et al. Risk factors of treatment resistance in major depression: Association with bipolarity Journal of Affect Disord 2010; doi: 10.1016/j.jad. 2010.03.001.

11. Hirschfeld R.M.A., Cass A.R., Holt D.C.L., Carlson C.A. Screening for bipolar disorder in patients treated for depression in a family medicine clinic. J Am Board Fam Pract 2005;18:233–9.)