AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: NA
ACTIVE INGREDIENT: NA

Study No:
NIS-NAR-XXX-2013/1

Developmental Phase: NA
Study Completion Date: 25 Sep 2014
Date of Report: June 29, 2015

OBJECTIVES:

Primary objective

The primary objective of this NIS was to determine the percentage of patients with unipolar major depression that do not achieve remission after one antidepressant treatment by assessment of basal and post treatment HAM- D17.

Secondary objectives

Secondary objectives of the NIS were

To describe the socio-demographic characteristics of resistant depression patients by examination of age, gender, marital status, education level, employment status, cohabitation and type of health insurance at the first visit

To describe the clinical features of resistant depression patients by assessment of starting age, number of previous episodes, duration of current episode, type of symptoms (cognitive, affective, somatic), suicidal ideation or intention, clinical history, presence of substance abuse or dependence at the first visit.

To describe the treatment characteristics of resistant depression patients by assessment of treatment type (eg. pharmacological, psychosocial), type of drug, treatment duration, frequency of visits, treatment adherence at the end of the treatment

To describe the treatment expectations of resistant depression patients by assessment of patients expectations by means of the credibility/expectations questionnaire modified at the first visit.

To compare those features between patients that achieve or not the remission after one antidepressant treatment.

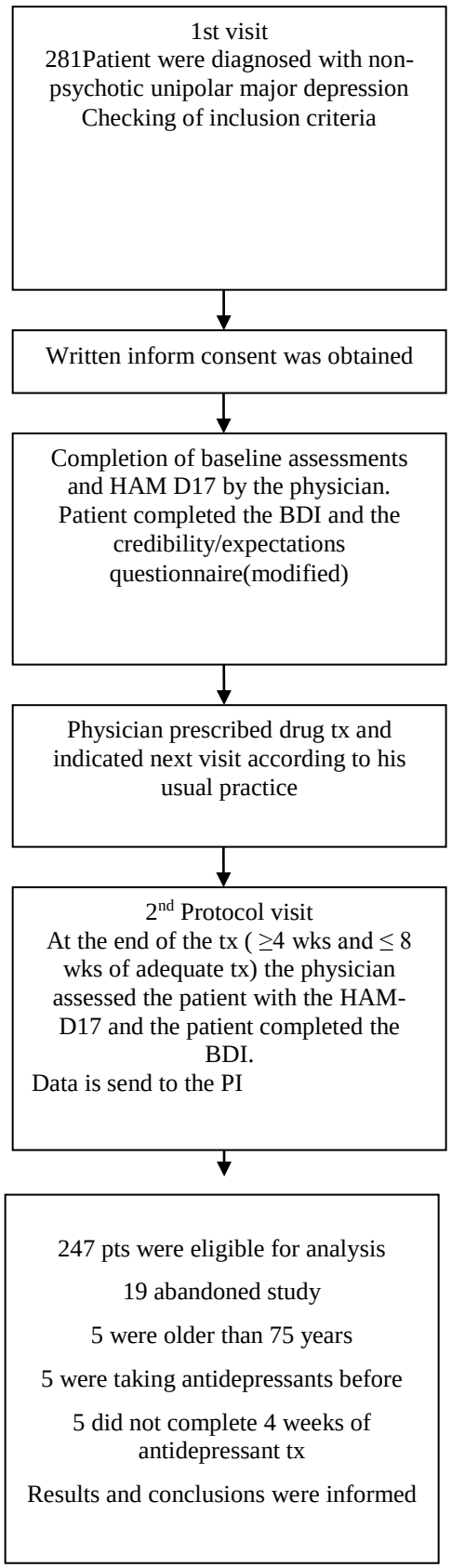
To compare the depression severity change assessed by the physician by means of the HAM D17 with the evaluation of the patient by means of the BDI.

METHODS:

Two hundred eighty one patients that were suffering of a non psychotic unipolar major depression episode were enrolled. At the first visit, after making the clinical diagnosis and checking the inclusion criteria the patient was be invited to enter to the study. Written informed consent was asked. Socio-demographic and clinical baseline features were assessed as usual practice and the patient was asked to complete the Beck Depression Inventory and the credibility/expectations questionnaire (modified). Afterwards the physician decided according to his current and usual practice and local rules the type of antidepressant that he prescribed to the patient as well as the dose, other concomitant medications, frequency of visits or if a psychosocial treatment was needed.

After the antidepressant treatment (no less than 4 to no more than 8 weeks after having achieved the antidepressant doses considered adequate by the physician) in another visit, the physician assessed again the severity of the depression by the HAM-D17 and the patient was invited to complete again the Beck Depression Inventory. All data was remitted to the PI who analysed it and got the results.

Figure 1 Study Flow Chart


1st visit
281Patient were diagnosed with non-psychotic unipolar major depression
Checking of inclusion criteria
Written inform consent was obtained
Completion of baseline assessments and HAM D17 by the physician.
Patient completed the BDI and the credibility/expectations questionnaire(modified)
Physician prescribed drug tx and indicated next visit according to his usual practice
2nd Protocol visit
At the end of the tx (≥4 wks and ≤ 8 wks of adequate tx) the physician assessed the patient with the HAM-D17 and the patient completed the BDI.
Data is send to the PI
247 pts were eligible for analysis
19 abandoned study
5 were older than 75 years
5 were taking antidepressants before
5 did not complete 4 weeks of antidepressant tx
Results and conclusions were informed

Inclusion criteria

The subject population that were observed in the NIS, must fulfilled all of the following criteria:

1. Female and male aged 18 to 75 years old
2. Outpatients with a current episode of non-psychotic unipolar major depression according to the DSM IV-TR
3. Severity of illness assessed by means of a score ≥ 14 in the HAM D17
4. Have not been medicated for the current depression episode with an antidepressant
5. Provision of subject informed consent

The prescription of the medicinal product was clearly separated from the decision to include the subject in the NIS.

Exclusion criteria

1 Subjects that were participating in any clinical trial, could not take part in this study.

2. Individual that participated in the last 3 months (including this study) or was participating in a clinical trial.

Target patient population

Target population was unipolar depressed patients treated by psychiatrists in Argentina. Two hundred eighty one patients were recruited by 23 investigators with a mean of 12 patients by each investigator. The maximum of patients recruited by an investigator was 30 and the minimum was 1.

The minimum sample size designed previously was 214 subjects. The sample size was calculated for a confidence level of 95% (α=0.05) and a margin of error of 6% estimating the proportion of 72% of subjects that will not achieve remission (primary outcome variable) after one antidepressant treatment as observed in a previous study (Trivedi et al, 2006).

The estimation of the sample size has been calculated with the following equation:

$$N = \frac{Z^2 . p.q}{e^2}$$

where Z =1.96 (for 95% confidence); p is the expected proportion (0.72); q is equal to 1-p and e is the margin of error (0.06).

Criteria for evaluation (main variables)

Primary variable

The primary variable was presence or absence of remission. It was measured by means of the HAM-D17 score. All patients that achieved a score ≤ 7 in the HAM D17 were considered in remission. Hamilton Rating Scale for Depression is a questionnaire for the assessment of severity of depression in patients previously diagnosed. It is valued by means of data of a psychiatric interview and accepts complementary data of secondary sources. Although its first version had 21 items (Hamilton, 1960), a reduced version was done with 17 items (Hamilton, 1967) that is recommended by the National Institute of Mental Health. Spanish adaptation and validation was done in 1986 by Ramos-Brieva (1986).

Each question has 3 or 5 possible answers, with a score of 0-2 or 2-4 respectively. Total score is between 0 to 52.

Secondary variables

1. Socio demographic variables (gender, age, marital status, cohabitation, education level, type of health insurance, employment status) were collected by questioning the patient.

2. Clinical Variables:

a. starting age, number of previous episodes, duration of current episode, presence of physical illness, presence of substance abuse or dependence was asked during the interview.

b. Type of symptoms (cognitive, affective, somatic, suicidal ideation or intention) was collected by means of questions in the interview and the BDI (Beck Depression Inventory).

The Beck Depression inventory is a self administered questionnaire created by Aaron Beck which has 21 questions with 4 possible answers. It is an instrument that measures severity of depression. It is composed by items related with affective symptoms as hopelessness and irritability, cognitive symptoms as low self esteem and guilt and

somatic symptoms as fatigue and weight loss. BDI II was adapted to Argentina by Brenlla and Rodriguez (2009)

3.Expectations of the treatment: Was collected by means of the credibility/expectations questionnaire modified.

4.Therapeutic variables: Drug and dose used. Duration of untreated episode. Time to remission. Number of visits, psychosocial treatment.

RESULTS:

Population Analysis Sets:

Definition of the target population

The sample consisted of 281 patients recruited in 20 sites by 23 investigators. Only 247 were included in the statistical analysis. Nineteen abandoned the study, 5 did not completed at least 4 weeks of antidepressant treatment and 10 were wrongly included in the study (5 because they have taken antidepressant for the current depressive episode and 5 because they were older than 75 years).

Statistical Analysis Result

Descriptive Analysis:

Description of the sample

The sample consisted of 247 patients. 32.8% were men (n=81) and 67.2% were women (n=166). Mean age was 46.67 ± 14.45 (range 18- 75). Marital status was the following: 27.9% were singles (n= 69), 50.6% were married or living with their fiancé/e (n= 125), 15.8% were separated or divorced (n = 39) and 5.7% were widows (n = 14). Education level was high: 0.4% had not finished their elementary school (n= 1), for 10.1% was the highest level achieved (n= 25), 49% finished high school (n= 121) and 40.5% completed the university or a tertiary career (n= 100). Employment status was the following: 17.4% was unemployed (n= 43), 50.6% was employed (n= 125), 20.2% were self employed (n= 50) and 11.7% were retired (n= 29).

Almost twenty three percent lived alone (22.8%, n = 56) and 77.2% lived with other/s person/s (n= 190). Six percent had no medical insurance (6.1%, n= 15), 32.1% had a private health insurance (n= 79) and 61.8% had union´s health insurance (n= 152). Only 7.3% (n= 18) had abuse or dependence to drugs. Almost half of the sample had an organic illness (48%, n= 118) and took medications (49.2%, n= 125) such as antihypertensives, fibrates and statins, analgesics, thyroid hormone and proton pump inhibitors principally.

Median of number of previous depressive episodes was 1 (range 1-10). Years since the first episode was 7.83 ± 10.36 (range= 0- 49).

Duration of antidepressant treatment was 44.26 ± 12.35 (range = 27-86). Antidepressants used were Escitalopram (42.9% n= 106), sertraline (18.2% n=45), paroxetine (13.7% n=

34), desvenlafaxine (8.9% n= 22), agomelatine (4 % n=10), fluoxetine (3.6% n= 9), venlafaxine (2.4% n= 6), bupropion (2% n= 5), mirtazapine (1.2% n= 3), duloxetine (1.2% n=3), clorimipramine (0.8% n= 2), fluvoxamine (0.4% n=1) and citalopram (0.4% n=1).

Sixty six percent had also psychotherapeutic treatment (n =163). Related to treatment expectancy and credibility, it was high being 74.15± 18.20 the mean credibility of the treatment (in a 0-100 scale),7.17 ± 1.81 the mean feeling of usefulness of the treatment (in a 0-10 scale) and 75.02 % ± 17.28 % the feeling of the improvement that would be achieved.

Description of non remitted patients

46.6 % of the patients treated did not achieve remission after antidepressant treatment. These patients had a mean age of 48.31 ± 14.53 years old (20-75), their age at the first episode was 39.46 ± 14.53 years old(17-75). One third were men (30.4% n= 35) and 69.6% were woman (n= 80).

Marital status was the following: 22.6% were singles (n= 26), 52.2% were married or living with their fiancé/e (n= 60), 19.1% were separated or divorced (n = 22) and 6% were widows (n = 7). Education level was high: For 10.4% elementary level was the highest level achieved (n= 12), 43.5% finished high school (n= 50) and 46.1% completed the university or a tertiary career (n= 53). Employment status was the following: 15.7% was unemployed (n= 18), 48.7% was employed (n= 56), 21.7% were self employed (n= 25) and 13.9% were retired (n= 16).

A percentage of 19.1 lived alone (n = 22) and 80.9% lived with other/s person/s (n= 93). 3.5% percent had no medical insurance (n= 4), 32.2% had a private health insurance (n= 37) and 64.3% had union´s health insurance (n= 74).

Median of number of previous depressive episodes was 1 (range 0-10). Years since the first episode was 8.85 ± 10.7 (range= 0- 49).

With respect to the current episode, the duration of it was of 44.1 ± 11.79 days (28-76). A percentage of 20 (n= 23) had suicidal ideas and 40.9% (n= 47) had death ideas. No one had done suicidal intents during the current episode. With respect to cognitive symptoms, ninety three percent had loss of interest (n= 107), a percentage of 89.6% had low self esteem (n0 103), 88.7% (n= 102) had apathy, 88.7% (n= 102) were sad, 85.2% (n= 98) had anhedonia. Hopelessness was felt by 73.9% (n=85) of non remitted patients, as well as guilt (70.4%, n= 81) and indecisiveness (63.5%, n= 73). With respect to somatic symptoms, 86.1% (n= 99) had loss of energy or fatigue, 82.6% (n= 95) had decreased concentration and 75.7% (n = 87) had insomnia, 73.9% (n= 85), loss of libido, 69.6% (n= 80) irritability, 61.7% (n= 71) had spontaneous or easy crying, 47.8% (n= 55) had loss of weight while 27% (n= 31) had weight gain. A percentage of 44.3% had psychomotor retardation (n= 51), while 24.3% (n= 28) had psychomotor agitation. Only one fifth (20%, n= 23) had hypersomnia.

Only 10 patients had abuse or dependence to substances (8.7%). More than half the patients had organic illness (52.2%, n = 60) and took medication (53%, n= 61).

The following Antidepressants were used: Escitalopram (43.5% n= 50), sertraline (15.7% n=18), paroxetine (13% n= 15), desvenlafaxine (11.3 % n= 13), agomelatine (4.3% n=5), fluoxetine (3.5% n= 4), bupropion (3.5% n= 4), venlafaxine (2.6% n= 3), clorimipramine (1.7% n= 2) and fluvoxamine (0.9% n=1). Number of visits was 3.08 ± 1.76 (0-9)

A percentage of 62.6% (n=72) had received psychotherapeutic treatment. 41.66% received support therapy (n= 30), 29.16 % (n= 21) received cognitive –behavioral therapy, 23.61% (n= 17) received psychoanalytic therapy and 5.55% (n= 4) received other type of therapy.

The adherence to medication was in general good. Only 1.7% (n=2) had none adherence, 7% (n=8) had low adherence, 7.8% (n= 10) had moderate adherence, 50.4% (n= 58) had good adherence and 33% (n= 38) had high adherence to medication.

Treatment expectations and credibility

It have been measured treatments expectations by means of a modified version of the CEQ (Credibility/ expectations questionnaires). Rational credibility was measured by questioning how much the subject thought the treatment would improve his depressive symptoms. Non remitted patients had a mean score of 71.42 % ± 19.58 (in a 0 to 100% scale). A percentage of 20.5% had a treatment credibility low or equal to 50%. Affectively based expectancy was measured by two questions. The first asked about the feelings of how much would the treatment help to reduce the symptoms. Mean score was 7.16 ± 1.64 (in a 0 to10 scale). Seventeen percent of non remitted patients had anexpectancy less or equal to 5. The second question was about how much would be the improvement after the treatment. Mean score was 74.73 ± 17.08 (in a 0 to100% scale). A percentage of 12.5% felt that the improvement would be lower or equal to 50 %.

Comparison between remitted and non remitted patients

a)Sociodemographic features

There were no differences in age (Remitted[R] 45.24 ± 14.4 vs Non Remitted [NR] 48.31 ± 14.36, $t(245) = -1.6$, $p = 0.09$), sex ($X^2(1)= 0.54$, $p = 0.46$), civil status ($X^2(3)= 3.87$, $p = 0.27$), education level ($X^2(3)= 3.89$, $p = 0.27$), employment status ($X^2(3)= 1.64$, $p = 0.65$), cohabitation ($X^2(1)= 1.62$, $p = 0.20$) and health insurance ($X^2(2)= 2.65$, $p = 0.26$).

b) Clinical features

The only differences in signs and symptoms of the recent depressive episode was that more non remitted patients had death ideation (R: 28.8% vs NR: 40.9%, $X^2(1)= 3.97$, $p = 0.04$ and suicidal ideation (R: 10.6% vs NR: 20%, $X^2(1)= 4.25$, $p = 0.03$). Furthermore, more remitted patients had sadness during their recent episode (R:96.2% vs NR: 88.7%, $X^2(1)= 5.13$, $p = 0.02$). No other symptoms differences were recorded (Table 1). However, the depression of non remitted patients was more severe as measured by the Hamilton Depression rating scale during the first visit (R: 18.67 ± 3.8 vs NR: 20.66 ± 4.63, $t(245)= -3.69$, $p < 0.001$) and the Beck Depression inventory (R: 27.38 ± 8.41 vs NR: 31.83 ± 9.82, $t(245.9)= -3.7$, $p < 0.001$).

There were no differences in substance abuse or dependence (R: 6.1% vs NR: 8.7%, $X^2(1)= 0.63$, $p = 0.42$) , frequency of organic illness (R: 43.9% vs NR: 52.2%, $X^2(1)= 1.51$, $p = 0.21$) or medication use (R: 45.8% vs NR: 53%, $X^2(1)= 1.28$, $p = 0.25$).

There was no difference in age of first episode (R: 38.29 ± 13.13 vs NR: 39.46 ± 14.53, $t(245)= - 0.66$, $p = 0.50$), but non remitted patients had more previous depressive episodes (R: 1.10 ± 1.38 vs NR: 1.59 ± 1.62, U de Mann Whitney 5958, $Z=-2.63$, $p= 0.008$). While only 38.6% of first depressive episode patients didn´t achieve remission (34 individuals of 88), 44.6% of second episode patients didn´t get remission (29 individuals of 65) and 55.6% of third or higher number of episodes patients had not remitted.

c) Treatment expectations

Remitted patients had more credibility in the treatment proposed (R: 76.48 ± 16.82 vs NR: 71.42 ± 19.58, $t(241)= 2.16$, $p = 0.03$). No differences were observed in expectations feelings of symptoms reduction or improvement ($t(241) = 0.05$, $p = 0.95$ and $t(241)= 0.24$, $p = 0.81$ respectively).

d)Treatment features

There were no differences in type of antidepressant used ($X^2(15)= 16.2$, $p = 0.36$), percentage of patients treated with psychotherapy (R:68.9% vs NR: 62.6%, $X^2(1)= 1.09$, $p = 0.29$) or type of psychotherapy used within these patients ($X^2(4)= 2.65$, $p = 0.61$). Treatment duration was similar between remitted and non remitted patients (R: 44.4 ± 12.86 vs NR: 44.10 ± 11.79, $t (245)= 0.18$, $p =0.85$) as well as number of visits until the last study evaluation (R: 3.14 ± 1.64 vs NR: 3.08 ± 1.76, $t(245)= 0.26$, $p = 0.79$). Treatment adherence was higher in remitted patients than in non remitted (no adherence R:0% vs NR: 1.74%, low adherence R:0% vs NR: 6.9%, moderate R:3.8% vs NR: 7.8%, good adherence R: 40.9% vs NR: 50.4% and high adherence R:55.3% vs NR: 30%, $X^2(4)= 21.25$, $p < 0.001$).

We made a logistic regression model with remission as the independent variable and number of episodes, adherence, baseline HAM D score, treatment credibility and presence of sadness, suicidal ideation and death ideas as dependant variables. This model indicated that three of the factors considered above were significantly associated with probable remission. By strength of association (Odds ratio), these ranked: 1)lower baseline HAM D score, 2) higher adherence and 3) presence of sadness (Table 2).

Comparison between depression severity change reported by the patient or the physician

There was a positive correlation between the severity change reported by the patient (by means of the BDI and the one reported by the physician by means of the HAM D ($r= 0.732$, $p < 0.001$).

Severity change reported by the patient was lower than severity change reported by the physician (BDI: 54.38 ± 23.91% vs HAM D: 59.07 ± 23.07%, t (245)= -4.2, $p < 0.001$).

In a subanalysis we observed that while there was a difference between severity change reported by the patient and the physician in remitted patients (BDI: 66.9 ± 17.7% vs HAM D: 75.27 ± 10.59 %, t(130) = -6.65, $p < 0.001$), there was no difference between severity change report in non remitted patients (BDI: 40.11 ± 22.04% vs HAMD: 40.57 ± 19.21%, t (114)= -0.25, p = 0.79).

Table 1. Comparison of clinical signs and symptoms between remitted and non remitted patients

Depressive sign or symptom	Remitted patients (n=132)	Non Remitted patients (n= 115)	X^2Test
Psychomotor agitation	28.03% (37)	24.34% (28)	$X^2(1)= 0.43$, p = 0.51
Psychomotor retardation	39.39% (52)	44.34% (51)	$X^2(1)= 0.62$, p= 0.43
Weight gain	21.96% (29)	26.95% (31)	$X^2(1)= 0.83$, p= 0.36
Loss of weight	46.96% (62)	47.82% (55)	$X^2(1)= 0.01$, p= 0.89
Hypersomnia	15.9% (21)	20% (23)	$X^2(1)= 0.7$, p= 0.4
Insomnia	75% (99)	75.65% (87)	$X^2(1)= 0.01$, p= 0.9
Suicidal ideation	10.6% (14)	20% (23)	$X^2(1)= 4.25$, p= **0.03**
Suicidal intent	0.75% (1)	0% (0)	$X^2(1)= 0.87$, p= 0.35
Ideas of death	28.78% (38)	40.86% (47)	$X^2(1)= 3.97$, p= **0.04**
Low self esteem	81.81% (108)	89.56% (103)	$X^2(1)= 2.96$, p= 0.08
Guilt	71.21% (90)	70.43% (81)	$X^2(1)= 0.01$, p= 0.89
Hopelessness	68.18% (90)	73.91% (85)	$X^2(1)= 0.97$, p= 0.32
Apathy	88.63% (117)	88.69% (102)	$X^2(1)= 0.0$, p= 0.98
Decreased concentration	75.75% (100)	82.6% (95)	$X^2(1)= 1.7$, p= 0.18
Anhedonia	90.9% (120)	85.21% (98)	$X^2(1)= 1.92$, p= 0.16
Loss of interest	88.63% (117)	93.04% (107)	$X^2(1)= 1.41$, p= 0.23

Loss of energy or fatigue	85.6% (113)	86.08% (99)	$X^2(1)= 0.001$, p= 0.91
Indecisiveness	66.66% (88)	63.47% (73)	$X^2(1)= 0.27$, p= 0.6
Irritability	68.18% (90)	69.56% (80)	$X^2(1)= 0.05$, p= 0.81
Spontaneous or easy crying	56.06% (74)	61.73% (71)	$X^2(1)= 0.81$, p= 0.36
Loss of libido	77.27% (102)	73.91%(85)	$X^2(1)= 0.37$, p= 0.53
Sadness	96.21% (127)	88.69% (102)	$X^2(1)= 5.13$, p= **0.02**

Table 2. Logistic regression model. Factors associated with remission

Factors	**OR [95% CI]**	**X^2**	**p-value**
Lower Baseline HAM D score	1.12[1.04-1.20]	9.8	0.002
Higher adherence	0.43 [0.28-0.67]	14.3	< 0.001
Presence of sadness	0.20 [0.06-0.67]	6.8	0.009

Remission: HamD total score at last visit ≤ 7; OR: Odds Ratio; CI: confidence interval.

Associated factors are ranked by significance. Factors not associated: number of episodes, presence of suicidal ideation or death ideation, treatment credibility.