Non-Interventional Study (NIS) Report	
NIS Name/Code	NIS-NGR-XXX-2011/1
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NIS REPORT SYNOPSIS

A cross-sectional observational study to describe treatment management of patients with Major Depressive Disorder (MDD) and inadequate response to antidepressants in Greece (MADDRE STUDY)

Study dates:	**First Subject In:** 3rd quarter 2011 **Last Subject Last Visit:** 1st quarter 2012

Total planned study period	
Estimated date of First Subject In (FSI)	3rd quarter 2011
Estimated date of Last Subject In	1st quarter 2012
Estimated date of Last Subject Last Visit	1st quarter 2012
Estimated date of Data base lock	2nd quarter 2012

1. RATIONALE FOR CONDUCTING THIS RESEARCH STUDY

According to the international literature, the probability of achieving sustained remission in MDD with first-line pharmacotherapy is approximately 30%.This implies that more than two out of three patients with MDD require modification of the initial antidepressant treatment. The administration of adjunctive (add-on) therapy in patients with inadequate response to standard antidepressant therapy has been associated with improved effectiveness / response to therapy. The selection of the proper add-on therapy is done among several pharmaceutical agents (antidepressant, antipsychotic), whereas there are also alternative forms of treatment (e.g. psychotherapy, phototherapy, acupuncture) that have been used as adjunctive therapy with a favorable outcome for patients with MDD .
In Greece, there is a considerable lack of data on current clinical practice regarding a) sequenced therapy in MDD, b) clinical criteria underlying the choice of sequential therapies in case of insufficient response, and c) the choice of add-on therapy in MDD. In particular, the clinical and other criteria underlying the choice of the agent/intervention of adjunctive treatment as well as the effectiveness/outcome of these alternative approaches are very unclear. The investigation of the aforementioned data in real-life clinical setting in Greece comprises the research objective of this study.

The primary objective of this study was to document the effectiveness of the drug therapies administered as add-on treatment in patients diagnosed with MDD who had an inadequate disease control with standard antidepressant therapy. Effectiveness in the context of this study was defined as the percentage of patients who experienced response to treatment or disease remission, 4 weeks following the initiation of adjunctive (add-on) therapy.

2. OBJECTIVES

2.1 Primary objective

The primary objective of this study was the assessment of the response to add-on therapy at 4 weeks, in patients with MDD who had an inadequate disease control with antidepressants. The assessment of the response was performed with the estimation of the percentage of patients with a CGI-I score ≤ 2 at week 4 following the initiation of the add-on therapy (at study visit).

2.2 Secondary objectives

The secondary objectives of this study were the following:

- Description of the treatment algorithm (sequence of administered therapies) applied in routine clinical practice for the management of MDD patients until the initiation of add

on medication.

- Description of patient's clinical characteristics which guided clinician's selection of add-on treatment.
- Description of add-on treatments administered in routine clinical practice.
- Assessment of the severity of depressive symptoms based on MADRS scale, 4 weeks after the commencement of add-on medication.
- Estimation of the percentage of patients who experienced remission of depressive symptoms (defined as MADRS score ≤ 10) 4 weeks after the commencement of add-on medication.
- Estimation of the change in severity of depressive symptoms 4 weeks following the initiation of add-on medication for the population of patients with available baseline data (MADRS score prior to add-on medication onset).
- Estimation of the percentage of patients who responded to the add-on medication 4 weeks following its initiation (defined as change in MADRS score ≥ 50% compared to baseline score). This evaluation was made only for the population of patients with available MADRS score before the commencement of add-on treatment.

3. STUDY DESIGN AND SELECTION CRITERIA

This is a multicenter, cross-sectional observational study, during which data from a representative sample of 545 eligible patients who meet the inclusion criteria, was collected as described below. All required information for the purposes of this study was collected using paper or electronic Case Record Form (pCRF or eCRF). The study included 55 hospital and private practice sites, each of which enrolled 10-12 patients. The study was completed in a single visit, which took place within the normal clinical practice setting. The procedures of the study are shown in Table 1.

3.1 Inclusion criteria

The patients that were assessed in the context of this Study, should have fulfilled all of the following criteria:

1. Patients able and willing to participate in the study after providing written informed consent.
2. Inpatients and outpatients of either gender, aged between 18 and 65 years (including

limits).

3. Diagnosis of MDD (as per DSM-IV).

4. Patients with an inadequate disease control during antidepressant therapy.

5. Patients who already receive add-on therapy and have completed 4-5 weeks of treatment at the time of their enrolment in the study.

The prescription of the medicinal products was clearly separated from the decision to include the patient in the study.

3.2 Exclusion criteria

Any of the following was considered as an exclusion criterion for the study:

1. Patients fulfilling criteria for diagnosis of any other psychiatric condition (except for MDD), as per DSM-IV Axis I, concomitant organic mental disorder or mental retardation.
2. Substance abuse or dependence (with the exception of nicotine dependence), as defined by DSM-IV criteria.
3. Participation in another study.

Assessment	Visit 1 4 weeks after the add-on therapy initiation *(+ 1 week)*
Informed Consent	X
Inclusion/exclusion criteria	X
Socio-demographic and anthropometric characteristics	X
Smoking & alcohol consumption history	X
Medical history	X
Family psychiatric history	X
Major Depressive Disorder history	X
Information on current MDD episode	X
Prior medication for the current MDD episode	X
Reasons for inadequate response for the current MDD episode	X
Patient's clinical characteristics that led to the choice of adjunctive treatment	X
Record of MADRS score at the commencement of adjunctive treatment (if available in patient's medical file)	X
Adjunctive (add-on) treatment for the current MDD episode	X
Assessment of the response with the use of CGI-I scale	X
Evaluation of the severity of depressive symptoms based on MADRS scale	X

Table1 Study Flow Chart

4. STUDY PLAN AND PROCEDURES

Patients were assessed at a single visit, 4 weeks (up to 5 weeks maximum) after the initiation of adjunctive therapy. The response of patients to adjunctive therapy was assessed using the CGI-I scale at 4 weeks, through which physician's impression regarding the improvement of patient's clinical state will be reflected. Furthermore, the MADRS scale was used as an additional measurement tool. For patients with available MADRS score at the start of adjunctive treatment, the change in MADRS score at week 4 was evaluated. In particular, an improvement in MADRS score greater than or equal to 50% indicates response, while remission is reflected when the total MADRS score is ≤ 10. In general, the response in the context of this study is defined as the percentage of patients with a CGI-I score ≤ 2.

The study included both inpatients and outpatients diagnosed with MDD according to DSM-IV criteria. Patients who had demonstrated remission of depressive symptoms after the consecutively administered treatments, entered the study. As this is an observational study, no specific treatment protocol was applied.

The treatment administered to study participants was fully consistent with the approved SmPCs of the administered medications and was based on the clinical discretion of the treating physician. The study was conducted under real-life conditions of daily clinical practice.

5. TARGET PATIENT POPULATION AND SAMPLE SIZE

This study included 545 inpatients and outpatients, aged 18-65 years, of both genders, diagnosed with major depressive disorder as per the DSM-IV criteria who had poor disease control during antidepressant treatment and were already receiving adjunctive (add -on) treatment and have completed 4 weeks of add-on drug therapy at enrolment in the study.

6. CRITERIA FOR EVALUATION (MAIN VARIABLES)

6.1 Primary variable

The primary outcome variable in this study was the percentage of patients with CGI-I score ≤ 2 at study visit {Week 4 after the commencement of additional (add-on) treatment}.

6.2 Secondary variables

- Mean CGI-I score of all patients at the study visit (4 weeks following the initiation of adjunctive drug therapy).

- Number of consecutive treatments administered for the management of the current MDD episode until the commencement of adjunctive (add-on) medication. Percentage of patients (n, %) treated with 1, 2, ≥3 consecutive pharmacological treatment strategies with inadequate response before the initiation of adjunctive drug therapy.

- Category of antidepressants received by the patients before initiating the add-on medication and percentage of patients (n,%) by sub-category of antidepressant drugs and order of sequence.

- Patients' clinical characteristics that guided clinician's selection of adjunctive (add-on) pharmacotherapy. Among the clinical characteristics that might influence the treating physician in selecting the adjunctive treatment the following are included: a) severity of the current MDD episode, b) number of sequenced antidepressant treatments for this episode, before the initiation of adjunctive treatment, c) number of relapses during the treatment of previous MDD episodes (if applicable), d) poor patient compliance to antidepressant treatment administered for the current episode of MDD.

- Categories of drugs used as adjunctive (add-on) therapy.

- Mean MADRS score of all patients at the study visit (4 weeks following the initiation of adjunctive therapy).

    - Percentage of patients (n, %) with MADRS score ≤ 10 at week 4 following the onset of adjunctive medication.

- Percentage of patients (n,%) with a change (decrease) in MADRS score ≥ 50% at week 4 following the initiation of adjunctive drug therapy. This figure will be calculated for the subgroup of patients with available MADRS score in their medical records at the initiation of adjunctive treatment.

This study was a purely non-interventional study and did not include any intervention in daily clinical practice, and in accordance with the protocol no safety data collection is foreseen, and there was no specific drug under investigation.Therefore, no pro-active safety data collection should have taken place. Only spontaneously mentioned safety events should have been reported as required by the post-marketing pharmacovigilance regulations. The methods for reporting spontaneously mentioned safety events are described below. It is of utmost importance that all staff involved in the study is familiar with the contents of this section. The investigator is responsible to ensure this.

7. STATISTICAL METHODS

Following scanning and indexing of all pCRFs and DQFs the DMC ensure that data are entered into the study database in accordance with the DEI, and that any data issues identified through online edit checks are handled as stated in the DEI. This is a Non-

Interventional/Research Study in which epidemiological methods including other methods are used for the analysis of human population health data.
Descriptive statistical analysis is performed for all study data and epidemiological methods were applied. Continuous variables are summarized with the use of descriptive statistical measures [mean value, standard deviation (SD), first and third quartiles (if necessary) and extreme values]. The normality of distribution of continuous variables is examined using Kolmogorov Smirnov test (K-S test) or Shapiro-Wilk test in order to determine whether or not to use parametric methods for the analysis of the sample data.

Categorical/distinct variables are displayed as frequency tables (N, %).
Association between categorical variables is assessed using either X^2 (chi-square test) or Fisher exact test, when appropriate. Furthermore, in order to examine the differences in mean values of continuous variables at different time periods, paired t-test is used.
All statistical tests presented in this report are two-sided and are performed at a 0.05 significance level.
The interpretation of all results is performed in a descriptive manner and missing data are not replaced.

7.1 Population Analysis Sets:

7.1.1 Definition of the target population

This study was expected to include 560 inpatients and outpatients, aged 18-65 years, of both genders, diagnosed with major depressive disorder as per the DSM-IV criteria who had poor disease control during antidepressant treatment, are already receiving adjunctive (add -on) treatment and have completed 4 weeks of add-on drug therapy at enrolment in the study. Efficacy evaluable analysis set (EV set) consists of all patients that have entered the study and have an evaluable final assessment based on the CGI-I scale. Patients that have not provided a final CGI-I measurement or their assessment is missing are not included in this analysis set. 545 patients in total entered the study. All 545 patients have a recorded 4 week score based on the MADRS scale. Only 74 patients out of 545 in total have a recorded baseline MADRS score and a final 4 week MADRS assessment. There were no patients that failed to meet either inclusion or exclusion criteria defined for this study.

7.1.2 Determination of sample size

Sample size calculation has been based on study's primary endpoint, which is the determination of the response of MDD patients to add-on therapy at 4 weeks, expressed as the percentage of the study population with a CGI-I score ≤ 2 (very much improved or much improved). Based on available published bibliographic data, it has been assumed that this response rate will be approximately 55%. Consequently, the assessment of 504 patients is required in order to estimate the aforementioned rate with an accuracy (confidence interval) of ± 4.34% at the study population. With expected probability of response rate 55% and sample size n=504, the 95% CI will range from 50.66 to 59.34 (dichotomous variable probability p=0.55, RSE=4.03%, a=0.05, 95% CI: 0.5066-0.5934). In the context of this sample size calculation, withdrawal rate has not been taken into account since according to the cross-

sectional study design only one visit is planned to be performed for the collection of the required data. However, taking into account that approximately 10% of patients will not provide evaluable data for various reasons such as missing data etc, approximately 560 patients are finally required to be enrolled in order to ensure the aforementioned sample size for the final statistical analysis.
The analysis population used for each part of the analysis are specified in the SAP and mentioned in each output. Three analysis sets are used for the analysis of this study. All three analysis sets are defined below.

Table 2 Analysis Sets ITT

Table 2. Analysis Sets ITT	
Parameter	**Total Number of Patients (N = 545)**
ITT analysis set	545
Per Protocol analysis set	545
Primary analysis set	74

Based on the definition of the populations used for this analysis and according to Table 2, there were 545 patients in total that entered the study. All 545 patients had a recorded MADRS scale at study visit. Only 74 patients out of 545 in total have a recorded baseline MADRS score and a final 4 week MADRS assessment. There were no patients that failed to meet either inclusion or exclusion criteria defined for this study.

7.2 RESULTS

7.2.1 Descriptive Analysis:

Demographic and Other Baseline characteristics

Based on the results presented on Table 3 below we can highlight the following.

- On average the patients that participated the on the study are 44 years old. The youngest patient is 18 years old and the oldest 65 years old.
- The participation of female patients (342 (62.8%)) is almost two times higher than male participation (203 (37.2%)).
- BMI average value of 26.1 can be deemed to be laying within normal ranges

Table 3 Demographic Characteristics

Table 3 Demographic Characteristics ITT set	
Parameter	**Total number (N=545)**
Age (years)	
N	545
Mean	44.0
Standard Deviation	11.39
Minimum	18.0
Maximum	65.0
Gender n(%)	
Female	342 (62.8%)
Male	203 (37.2%)
Race n(%)	
Black	1 (0.2%)
White	544 (99.8%)
Height (cm)	
N	545
Mean	169.5
Standard Deviation	8.66
Minimum	150.0
Maximum	198.0
Body Weight (kg)	
N	545
Mean	75.2
Standard Deviation	14.45
Minimum	45.0
Maximum	148.0
BMI (kg/m2)	
N	545
Mean	26.1

Table 3 Demographic Characteristics ITT set	
Parameter	**Total number (N=545)**
Standard Deviation	4.10
Minimum	16.9
Maximum	44.7

7.2.2 Primary Objective: Efficacy assessment of add-on treatment

Based on the results on the table 4 below we can comment on the following.

- Based on the CGI scale the entire number of patients (545) have scored on average a 2.1 score. Based on the benchmark defined for the CGI scale there were 402 responders (73.8.%) that recorded a score of CGI <= 2. In addition there are 143 patients (26.2%) that recorded a score of CGI > 2 and are considered as non responders.
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Table 4 CGI_I measurement following 4 weeks of add on treatment

Table 4. CGI_I measurement following 4 weeks of add on treatment ITT set		
Parameter	**Total number (N=545)**	**95 % CL**
CGI		
N	545	
Mean	2.1	(2.05 , 2.18)
Standard Deviation	0.77	
Median	2.0	
Minimum	1.0	
Maximum	5.0	
Response rate, n (%)		
CGI <= 2	402 (73.8%)	(70.0 % , 77.5%)
CGI > 2	143 (26.2%)	

7.2.3 Secondary objectives

Based on the results presented on table 5 below we can highlight the following.

- The non MDD related Medical current condition that stands out is Hypertension, which is present on 49 patients (9.0%). Furthermore the next more frequent current conditions are Diabetes Mellitus 14 patients (2.6%), Hypothyroidism 16 (2.9%) patients and Hypercholesterolaemia 10 patients (1.8%).

- For the purposes of the analysis 2 groups were identified regarding patients history

    - **Endocrine, nutritional and metabolic diseases (A)**, with patients of the following recorded current conditions: Diabetes Mellitus, Diabetes Mellitus type II, Obesity, Phaeochromocytoma, Polycystic Ovaries, Thyroid, Thyroid Cancer, Thyroid Nodules, Thyroid disease, Thyroid Alopecia, Cholesterolaemia, Hypercholesterolaemia, Hyperlipidemia, Hyperthyroidism, Hypothyroidism, Triglyceridemia (57 patients)

    - **Diseases of the circulatory system (B)** with the following recorded current conditions: Coronary Heart Disease, Heart Failure, Hypertension, Mitral Prolapse (55 patients)

    - **OTHER (C)** with all other recorded current conditions not included in the A and B groups (80 patients)

Table 5 Non MDD related Current medical condition **ITT set - Groups**	
Preferred diagnosis Term	**Total N=545**
All Current Conditions	192 (35.2%)
A	57 (10.5%)
B	55 (10.1%)
C	80 (14,7%)
Percentages are presented based on total number of patients enrolled in the study (545)	

History of Major Depressive Disorder

Based on the results of table 6 below we can highlight the following.

- The average time since initial diagnosis for the total number of patients participating in the study is 6 years. This time varies from a range of 0 to 42 years.
- The diagnosis based on the DSM was mainly (359 patients / 65.9%) due to a relapsing disorder. About one third of cases (186 patients / 34.1%), is characterized as a unique first incident.
- Regarding these cases characterized as relapsing disorder, on average 4 previous depression episodes were experienced.
- 470 patients (86.2%) did not require any hospitalization. On the other hand 75 (13.8%) required hospitalization. These patients spent on average approximately 1 month on site.
- 41(7.5%) had made at least one attempt.

Table 6. MDD Disease history ITT set	
Parameter	**Total number (N=545)**
Time since initial diagnosis (Years)	
N	545
Mean	6.0
Standard Deviation	7.79
Minimum	0.0
Maximum	41.9
DSM IV diagnosis, n (%)	
Relapsing disorder	359(65.9%)
Unique (first) episode	186(34.1%)
Number of Previous depression episodes	
N	357
Mean	4.1
Standard Deviation	4.53
Minimum	0.0
Maximum	63.0
Unknown Values (excluded)	2

Table 6. MDD Disease history ITT set	
Parameter	**Total number (N=545)**
Treatment type of previous depression episodes, n (%)	
Exclusive Coadministration	72 (13.2%)
Exclusive monotherapy	131 (24.0%)
Monotherapy and Coadministration	156 (28.6%)
Time since most recent recurrence/relapse (days)	
N	356
Mean	373.7
Standard Deviation	597.3
Minimum	20
Maximum	7300
Unknown Values (excluded)	3
Previous hospitalization, n (%)	
No	470 (86.2%)
Yes	75 (13.8%)
Number of previous hospitalization	
N	75
Mean	1.93
Standard Deviation	1,24
Minimum	1
Maximum	7
Average Time of hospitalization (days)	
N	75
Mean	28.3
Standard Deviation	17.3
Minimum	1
Maximum	90.0

Table 6. MDD Disease history ITT set	
Parameter	**Total number (N=545)**
Suicidal attempt, n (%)	
No	504 (92.5%)
Yes	41 (7.5%)
No of suicides	
1	26 (4,7%)
2	12 (2,2%)
3	1 (0,2%)
5	2 (0,4%)

Based on the results of table 7 below regarding the reasons of insufficient response to current MDD episode we can highlight the following.

- The three most frequent reasons of insufficient response to current MDD episode appear to be depressive mood recorded on 429 (78.7%) patients, stress on 369 (67.7 %) patients, sleep disorders on 349 (64.0%) patients.

Table 7. Description of patient's clinical characteristics contributing to the selection of add-on treatment ITT set	
Parameter	**Total number (N=545)**
Core depressive symptoms, n (%)	**510 (93.6%)**
Depressive mood	429 (78.7%)
Loss of interest or pleasure	254 (46.6%)
Lack of energy, fatigue	289 (53.0%)
Other MDD symptoms, n (%)	**521 (95.6%)**
Loss of appetite	163 (29.9%)
Sleep disorders	349 (64.0%)
Low self-esteem	212 (38.9%)

Table 7. Description of patient's clinical characteristics contributing to the selection of add-on treatment ITT set	
Parameter	**Total number (N=545)**
Guilt	186 (20.7%)
Psychomotor agitation/retardation	259 (47.5%)
Lack of concentration	269 (49.4%)
Suicide ideation	72 (13.2%)
Other reasons - clinical characteristics, n (%)	**457 (83.9%)**
Stress	369 (67.7 %)
Concomitant psychotic symptoms	65 (11.9%)
Severity of current MDD episode	179 (32.8%)
Insufficient treatment compliance	37 (6.8%)
Other	10 (1.8%)
Multiple records of the same category within each patient is counted only once.	
Percentages are presented based on total number of patients enrolled in the study (545)	

Information on the last depressive episode prior to enrolment

Based on the results of table 8 below we can highlight the following:

- Most of the patients had a current MDD episode that is either moderate in severity 226 (41.5%) or severe without psychotic features 238 (43.7%).
- 14 patients (2.4%) required hospitalization due to the current MDD episode.

Table 8. Current MDD episode ITT set	
Parameter	**Total number (N=545)**
Severity, n (%)	
Low	21 (3.9%)
Moderate	226 (41.5%)

Table 8. Current MDD episode ITT set	
Parameter	**Total number (N=545)**
Severe Without Psychotic Features	238 (43.7%)
Severe With Psychotic Features	60 (11.0%)
Hospitalization, n (%)	
No	531(97.4%)
Yes	14(2.6%)

Based on the results of table 9 below regarding the number for consecutive treatments received for current MDD episode prior to the initiation of add on therapy we can highlight the following.

- The total number of treatments received at different stages before the initiation of the add on therapy, 226 patients (41,5%) received 1 treatment line, 258 (47,3%) received 2 treatment lines and 61 patients (11,2%) received 3 treatment lines

Table 9. Consecutive treatments received for current MDD episode prior to the initiation of add on therapy ITT set	
Parameter	**Total number (N=545)**
Consecutive lines of treatment, n (%)	
1	226 (41.5%)
2	258 (47.3%)
3	61 (11.2%)

Table 10 Drug treatment category received before the initiation of add on therapy at any order.				
Antidepressant drug category	**# of Patients receiving drug at any order (N=545)**	**# of Patients receiving at 1st line**	**# of Patients receiving at 2nd line**	**# of Patients receiving at 3rd line**
SSRIs	**308 (56.5%)**	120	150	38
SNRIs	**230 (42.2%)**	80	115	35
TeCAs	**87 (16.0%)**	22	48	17
TCAs	**60 (11.0%)**	31	21	8
Other	**28 (7.0%)**	9	10	9
NDRIs	**20 (3.7%)**	2	12	6
Atypical Antipsychotic	**3 (0.6%)**	3	-	-
Lithium	**1 (0.2%)**	1	-	-

Information on add-on treatment

Based on the results on the table 11 below regarding the drug categories used for add on therapy we can comment:

- Atypical Antipsychotics is the most frequently used drug category in 470 (86.2%) patients, at least once as add on therapy during the course of the study.

Table 11. Drug categories used for add on therapy ITT set	
Parameter	**Total number (N=545)**
Add on therapy, n (%)	
Atypical Antipsychotic	470 (86,2%)
Other	42 (7,7%)
Buspirone	17 (3,0%)
Lithium	13 (2,4%)

Table 11. Drug categories used for add on therapy ITT set	
Parameter	**Total number (N=545)**
Psychostimulant	2 (0,4%)
Hormone T3	1 (0,2%)

More specifically based on the results on the table 12 below regarding the individual drug treatment used for add on therapy we can comment on the following:

- There were 23 different drugs that are used as add on therapy during the course of the study.
- In 13 patients 2 drugs were used in combination as add on therapy.

Table 12. Drug treatment used for add on therapy **ITT set**		
Parameter	**Total number (N=545)**	**Percentage %**
Add on therapy, n (%)		
Quetiapine	298	54,68
Olanzapine	80	14,68
Risperidone	37	6,79
Aripiprazole	36	6,61
Buspirone	16	2,93
Lithium	13	2,39
Pregabalin	14	2,57
Lamotrigine	9	1,65
Perphenazine	6	1,10
Ziprasidone	6	1,10
Paliperidone	5	0,92

Amisulpride	4	0,73
Valproate	4	0,73
Topiramate	3	0,55
Mirtazapine	2	0,37
Modafinil	2	0,37
Amitriptyline	1	0,18
Aripiprazole+Quetiapine	1	0,18
Carbamazepine	1	0,18
Haloperidol	1	0,18
Lamotrigine+Olanzapine	1	0,18
Lamotrigine+Ziprasidone	1	0,18
Liothyronine	1	0,18
Lithium+Quetiapine	1	0,18
Oxcarbazepine	1	0,18
Perphenazine+Quetiapine	1	0,18
Total	**545**	**100**

Secondary assessment MADRS

Based on the results on the table 13 below

- On MADRS scale the entire number of patients (545) have scored on average a 14.6 score. Based on the benchmark defined for the MADRS scale there were 220 responders (40.4%) that recorded a score of MADRS <= 10. In addition there are 325 patients (59.6%) that recorded a score of MADRS >10 and are considered as non responders.

- On the 95% for the mean MADRS score (13.9, 15.4) the total number of patients have scored on average significantly higher than the benchmark of 10. In addition the proportion of responders (response rate based on the benchmark of MADRS score of 10) is significantly lower than 50%, with a 95% C.I. (36.2%, 44.6%)

Table 13. MADRS measurement following 4 weeks of add on treatment
ITT set

Parameter	**Total number (N=545)**	**95 % CL**
MADRS		
N	545	
Mean	14.6	(13.9 , 15.4)

Table 13. MADRS measurement following 4 weeks of add on treatment ITT set		
Parameter	**Total number (N=545)**	**95 % CL**
Standard Deviation	8.60	
Median	14.0	
Minimum	0.0	
Maximum	48.0	
Response rate, n (%)		
MADRS <= 10	220(40.4%)	(36.2%, 44.6%)
MADRS > 10	325(59.6%)	

Based on the results on the table 14 below

- There are 74 patients that had a baseline score based on the MADRS scale. On average these 74 patients have a mean score of 24.8.
- At the end of the 4 week study period all the patients (545) have on average a MADRS score of 14.6.
- The difference between the average MADRS score recorded at baseline and at the end of the 4 week period of the study is 9.5. Based on the results the analysis this difference is significant (<.0001) at a significance level of 5%. As shown on the above table a 95% confidence interval for this difference is (6.7 , 12.4).

Table 14. Change from baseline MADRS measurement following 4 weeks of add on treatment Efficacy evaluable analysis set					
Parameter					
MADRS	Baseline	Week 4	Difference	p-value	95% C.I.
N	74	545	74		
Mean	24.8	14.6	9.5	<.0001	(6.7 , 12.4)
Standard Deviation	11.42	8.60	12.30		
Median	22.0	14.0	9.0		

Table 14. Change from baseline MADRS measurement following 4 weeks of add on treatment Efficacy evaluable analysis set					
Parameter					
Minimum	3.0	0.0	-23.0		
Maximum	47.0	48.0	39.0		

Based on the results on the table 15 below we can highlight the following:

- 31 patients have succeeded a 50% or more MADRS reduction in their score from baseline over the 4 week period of the study. These patients represent the 41.9% of the total number of patients that recorded a baseline score based on MADRS scale. Based on the 95% Confidence Limits (30.27% , 53.1%) the value of 50 is included in this interval providing significant evidence that there is no significant evidence of a reduction more than 50%.
- In addition patients that have managed to experience a reduction of less than 50% in their MADRS score over the 4 week period of the study are 43 representing a 58.1% of the total number of patients that recorder a baseline score based on MADRS scale.

Table 15 Change from baseline MADRS response rate following 4 weeks of add on treatment Efficacy evaluable analysis set		
Parameter	**Total number (N=74)**	**95 % CL**
MADRS change from baseline, n (%)		
Change < 50%	43(58.1%)	
Change >= 50%	31(41.9%)	(30.27%, 53.1%)

8. SAFETY

NA

9. ETHICS

The Study will be performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, the International Conference on Harmonization (ICH), Good Clinical Practice (GCP) and the applicable legislation on Research Studies.
The Investigator will perform the Study in accordance with the regulations and guidelines governing medical practice and ethics in the Greece and in accordance with the currently acceptable techniques and know-how.

9.1 Subject informed consent

The Investigator at each site will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the participation in the Study. Patients must also be notified that they are free to discontinue from the Study at any time. The patients should be given the opportunity to ask questions and allowed time to consider the information provided

10. DATE OF THE REPORT

05/03/2013