2. SYNOPSIS

Company name: ACRAF S.p.A.	TABULAR FORMAT REFERRING TO	(For National Authority Use Only)
Name of the finished product: Trazodone Contramid® OAD film-coated tablets	Volume:	
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Title of the study: A randomized, double-blind study comparing the efficacy and safety of trazodone OAD and venlafaxine XR in the treatment of patients with Major Depressive Disorder.

Study Coordinator: [redacted]

[redacted]

Publication (reference): not applicable

Study period (years): December 21st, 2012 (first patient-in) – April 25th, 2014 (last patient-out)	**Clinical Phase: III**

Objectives: The study objective was to evaluate the efficacy and safety of trazodone OAD vs venlafaxine XR after an 8-week treatment period in patients with major depressive disorder (MDD).

Methodology: This was a randomized, venlafaxine-controlled, double-blind, parallel design study in which a pre-treatment phase and a double-blind treatment phase were scheduled. Ten visits were scheduled: 1 in the Pre-Treatment Phase and 9 in the double-blind Treatment Phase. During the Pre-Treatment Phase, patients who signed the informed consent form underwent initial screening. Potential candidates were instructed to discontinue antidepressants or prohibited medications (wash-out) for a period specific to taper schedule (based on 5 elimination half-lives of the used medication). On the last day of the Pre-Treatment Phase, patients were evaluated for the final eligibility, and those qualified were randomly allocated to trazodone OAD 300 mg/day (1 week of tapering with trazodone OAD 150 mg/day) or to venlafaxine XR 75 mg/day once daily. During the double-blind Treatment Phase the patients were randomized to 8 weeks treatment with trazodone OAD or with venlafaxine XR. After 3 and 5 weeks of treatment, subjects were evaluated for the response. For non-responding patients dose was increased (in increments of 75 mg/day) till to reach the maximum of 225 mg/day for venlafaxine XR and 450 mg/day for trazodone OAD. Patients non-responding to treatment at the final visit had their study medication tapered from 1 to 3 weeks, according to the maximum dose reached during the study. In order to prevent relapse of depression symptoms, responders at the final visit might continue the treatment. In this case, an unblinded third party dispenser opened the treatment code and prescribed the same medication taken by the patients during the trial, according to the formulation available on the market. If symptoms or adverse events (AEs) became intolerable for the patient, dose adjustments were attempted after one week of dose increase. Efficacy and safety evaluations occured at Visit 2 (baseline), Visit 3 (7 days post-randomization; D7), Visit 4 (D21), Visit 6 (D35), Visit 9 (D56). Patients receiving increased dosages at the scheduled visits (Visit 4 and Visit 6) were strictly monitored for safety with further visits at Day 28, 42, 49 (Visits 5, 7, 8, respectively). If the treatment was judged unsuccessful and/or the tolerability unsatisfactory after dose adjustments, the Investigator discontinued the patients from the study and started another appropriate antidepressant therapy.

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Methodology:
Patients non responding at the final visit (Visit 9) were monitored for safety throughout the tapering period (Visit 10). If a patient discontinued early, he/she was asked to return to the clinic for the Treatment Early Termination Visit (TETV) as soon as possible, but no later than 1 week after discontinuation. All efficacy and safety evaluations were performed at the TETV.

Number of subjects: Recruitment of about 360 patients (180 patients per group) was planned

Diagnosis and Inclusion criteria: Patients meeting the following criteria were included in the study:
1) men and women 18-75 years of age (limits included) with no limitation of race; 2) outpatients; 3) MDD according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria as assessed using the MINI International Neuropsychiatric Interview; 4) 17-item Hamilton Depression Rating Scale (HAMD) score ≥ 18 at both screening and baseline visits with a decrease not exceeding 20% between screening and baseline; 5) symptoms of depression for at least one month before study entry (screening visit); 6) legally capable to give their consent to participate the study, and available to sign and date the written informed consent prior to the inclusion in the study; 7) women of childbearing potential had to agree not to start a pregnancy from the signature of the informed consent up to 30 days after the last administration of the investigational product;

Patients meeting the following criteria were not allowed to participate in the study:
1) participation in another trial involving any investigational drug during the past 60 days; 2) known hypersensitivity to venlafaxine or trazodone or their excipients; 3) use of venlafaxine or trazodone within the previous six months; 4) acute, or chronic, or recurrent medical conditions that might affect/jeopardize the study results; 5) significant liver disease, defined as active hepatitis or elevated liver enzymes > 3 times the upper boundary of the normal range; 6) significant renal disease, defined as urea and/or creatinine > 3 times the upper boundary of the normal range; 7) myocardial infarction within 6 months prior to start of the double blind treatment; 8) positive present history of glaucoma; 9) history of risk factors for Torsade de Pointes, such as heart failure, cardiac arrhythmias, bradycardia, cardiac conduction abnormalities, family history of long QT syndrome, cardiac hypertrophy, cardiomyopathy, chronic cardiac insufficiency; 10) values of electrolytes (sodium, potassium, calcium, magnesium, chloride) outside the normal laboratory range and judged clinically relevant by the Investigator; 11) concomitant treatment with drugs known for QT prolongation, or with drugs producing hypokalemia, or diuretics; 12) QTcF values higher than 450 msec in the electrocardiogram (ECG) performed at the screening; 13)n history of major depression resistant to medical treatments (previous failure to respond to two consecutive antidepressants of different classes used for a sufficient length of time at appropriate doses); 14) history of seizure events other than a single childhood febrile seizure; 15) history of alcohol or psychoactive substance abuse or addiction (except caffeine or nicotine) during the last year as defined by DSM-IV criteria; 16) positive urine drug screen for CNS-active drugs (cocaine, opioids, amphetamines and cannabinoids) at Visit 1 (screening); 17) acute risk of suicide (HAMD, criterion 3 with a value ≥ 3);

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Diagnosis and Inclusion criteria: 18) presence of any primary psychiatric disorder other than major depression;19) history or presence of bipolar disorder, any psychotic disorder, mental disorder due to general medical conditions; 20) pregnancy, lactation, or female with a positive urine pregnancy test result at Visit 1 (screening); 21) electroconvulsive therapy (ECT) within 30 days prior to the screening visit; 22) use of antipsychotic drugs within two months prior to the baseline visit (Visit 2); 23) use of any anxiolytic or sedative hypnotic drug within seven days prior to the baseline (Visit 2) and during the study. Exception was stable low doses of benzodiazepines for insomnia (if taken by the patient more than two weeks before the Treatment Phase); 24) use of any psychotropic drug or substance with central nervous system (CNS) effects within seven days prior to the baseline visit (Visit 2); 25) use of any non-psychotropic drug with psychotropic effects (e.g. β–adrenergic blockers) within seven days prior to the baseline visit (visit 2), unless a stable dose of the drug had been maintained for at least one month (three months for thyroid or hormonal medications) before the baseline visit (visit 2); 26) concomitant treatment with cytochrome P450 3A4 (CYP3A4) inhibitors (e.g. ketoconazole, ritonavir, indinavir); 27) hyperthyroidism, even if pharmacologically corrected; 28) start or discontinuation of psychotherapy within 6 weeks prior to screening; 29) clinically significant abnormalities on physical examination, vital signs, ECG, laboratory tests at the screening visit; 30) high blood pressure (supine systolic blood pressure [SBP] > 160 mmHg or supine diastolic blood pressure [DBP] > 90 mmHg) at screening or baseline, either untreated or under treatment with antihypertensives; 31) inability to comply with the protocol requirements, instructions and study-related restrictions; e.g. uncooperative attitude, inability to return for study-visits, and improbability of completing the clinical study; 32) vulnerable subjects (e.g. persons kept in detention); 33) if subject was the Investigator or his/her deputies, first grade relative, research assistant, pharmacist, study coordinator, other staff of relative thereof directly involved in the conduct of the study.

Test product, dose:
75 mg trazodone OAD capsules (Batches: 2011-9/S01 [expired date 30/09/2013]; 2012-5/S01, 2012-5/S10 [expired date 31/03/2015]; 150 mg trazodone OAD capsules (Batches: 2012-5/S01, 2012-5/S09 [expired date 31/03/2015]; 300 mg trazodone OAD capsules (Batches: 2011-9/S01 [expired date 30/09/2013]; 2012-5/S01; 2012-5/S05, 2012-5/S08, 2012-5/S11 [expired date 31/03/2015]
Reference product, dose: 37.5 mg venlafaxine extended release XR capsules (batches: 2011-9/S01 [expired date 30/09/2013]; 2012-5/S03, 2012-5/S01, 2012-5/S09 [expired date 31/03/2015]; 75 mg venlafaxine extended release XR capsules (batches: 2011-9/S01, 2011-9/S05, 2011-9/S03, 2011-9/S08 [expired date 30/09/2013]; 2012-5/S01, 2012-5/S02, 2012-5/S03, 2012-5/S07, 2012-5/S11, 2012-5/S09, 2012-5/S10 [expired date 31/03/2015].

Duration of treatment:
Test product, dose: 8 weeks (including 1 week 150 mg/day of dose-titration)
Reference product, dose: 8 weeks.

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Assessment criteria:
The primary study endpoint for clinical efficacy was the mean change from baseline (Visit 2-D0) in HAMD score at V9 (D56). The secondary study endpoints were: I) mean change from baseline (Visit 2-D0) in Montgomery-Asberg Depression Rating Scale (MADRS) score at Visit 9 (D56); II) Clinical Global Impression-Severity of Illness (CGI-S) and Clinical Global Impression-Global Improvement (CGI-G) at Visit 9 (D56); III) rate of responders defined as patients with a 50% decrease with respect to baseline on the HAMD score at Visit 9 (D56), IV) rate of remitters defined as patients with HAMD score ≤ 7 at Visit 9 (D56); v) safety and tolerability of trazodone OAD was compared to venlafaxine XR.

Statistical methods: Three study populations were defined for statistical analysis: the Intention-to-Treat (ITT) population defined as all randomized patients who took at least one dose of study medication, and having a baseline and at least one post-baseline 17-items HAMD total score assessment; the Per Protocol (PP) population defined as all randomized patients who had no major protocol violations, completed the study period (from V1 to V9) and had a 17-items HAMD rating at the end of the study period (V9) and the Safety Population defined as all patients who took at least one dose of the study medication.Study centres were pooled to obtain at least 10 patients in each pooled center. Data collected during the TET Visit were allocatedat the first missing visit after the last performed. Patients for whom the TET Visit was filled the same date scheduled for Visit 9 (dropped-out at V9) were considered completing the study and included in the PP population. Significance tests (two-sided) were performed at an alpha level of 5%. Secondary and other analyses were supportive in nature, therefore no adjustment for multiplicity was planned. All the efficacy parameters were analysed on the ITT population using the Last Observation Carried Forward (LOCF) imputation scheme for missing data and on the PP population. The primary efficacy end-point of the study was the demonstration of the non-inferiority of Trazodone OAD vs. Venlafaxine XR evaluated as change from baseline at Visit 9 on the 17-items HAMD total score. The parameter was analysed by an ANCOVA (analysis of covariance) model with baseline as covariate and treatment and pooled centers as sources of variation. The non-inferiority was fulfilled if the upper limit of the two-sided 95% confidence interval for the difference between treatments did not exceed the threshold of 3. The change from baseline at each post baseline visit of the HAMD total score, of the HAMD factors (anxiety/somatization, cognitive disturbance, retardation, sleep disturbance) and of the MADRS total score were analyzed by the same ANCOVA model (or analysis of variance [ANOVA] if the statistical assumpions underlying the ANCOVA were not satisfied. CGI-S and CGI-G were compared between groups using the Cochran-Mantel-Haenszel test stratified by pooled sites. Treatment groups were also evaluated treating the responses as continuous and applying the ANCOVA or ANOVA model. Responders and remitters were compared between treatment groups by a Cochran-Mantel-Haenszel test at each visit.Safety and tolerability assessments were performed on the Safety Ppopulation.

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Statistical methods: AEs were coded according to Medical Dictionary for Regulatory Activities (MedDRA) dictionary ver. 15.1. AEs were classified as AEs started on or after the first study medication administration date and AEs started prior to the first study medication administration date. Summaries of AEs started on or after the first study medication administration were presented as counts and percentages based on the number of patients exposed and compared by a Chi-square test or Fisher's exact test. Listing of pre-treatment and during treatment AEs were provided by treatment group displaying the description reported by the Investigator, the preferred term (PT) and the system organ class (SOC). Serious adverse events (SAEs), other significant AEs and deaths were listed and discussed with patient narratives. Separate listings were provided for pre-treatment SAEs and SAEs emerged during the study medication administration.
Each laboratory test was presented by descriptive statistics per treatment group, available visits and change from screening. Shift tables were calculated on the basis of Investigators' assessment (normal, altered but not clinically significant, altered and clinically significant). Pregnancy tests were listed.
Descriptive statistics were presented by treatment group for vital signs and body weight at each visit and on the change from baseline. 95% confidence intervals were also provided.
The number and percentage of patients with QTcF values higher than 450 msec or showing prolongation higher than 60 msec at any visit were provided and compared by a Chi-Square test or Fisher's exact test. The number and percentage of patients with an abnormal ECG assessed as clinically significant by the Investigator were provided for each treatment group at each visit.
The number and percentage of patients showing changes in the ECG evaluations with respect to the screening (from normal to abnormal) were provided for each treatment group at each visit.
Descriptive statistics on HR, RR, PR, QRS, QT, QTcB and QTcF were provided by treatment group at each available visit and on the changes from screening. Treatment groups comparison was performed by an ANOVA model at each visit. Changes from screening in physical examination were reported.

SUMMARY – CONCLUSION
Efficacy results: The aim of the present study was to compare the antidepressant efficacy of trazodone OAD, a prolonged-release formulation of trazodone indicated for the treatment of depressive disorders to venlafaxine XR, a well-known extended-release formulation of venlafaxine, one of the most prescribed antidepressant. Three hundred twenty one patients (165 in the trazodone OAD group and 156 in the venlafaxine XR group) were randomized and took at least one dose of the study medication. The ITT population consisted of 314 (162 in the trazodone OAD group and 152 in the venlafaxine XR group) who took at least one dose of the study medication, and had a baseline and at least one post baseline 17-items HAMD total score assessment. The PP population consisted of 249 patients (122 in the trazodone OAD group and 127 in the venlafaxine XR group) who completed the study period (from V1 to V9) and had the 17-items HAMD rating at the end of the study period (V9) without major protocol violations.

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Efficacy results: Patients enrolled in this study were significantly ill, as measured by validated clinical inventories.There were no clinically relevant or statistically significant differences between the treatment groups in patient demographics or clinical characteristics at baseline in all considered populations. The baseline mean severity of illness measured with HAMD-17 total score was at least moderate for both ITT and PP populations (ITT: Trazodone OAD 23.7 ± 3.42, Venlafaxine XR 23.8 ± 3.93; PP: Trazodone OAD 23.9 ± 3.41, Venlafaxine XR 24.1 ± 4.02). The baseline mean MADRS score was consistent with the HAMD-17 total score. Overall, the mean severity of illness was moderate and very close to severe, as defined by HAMD-17 cut off for severe depression (≥24). The primary efficacy measurement was the comparison of HAMD-17 scores reported at the Visit 9 with those reported at the baseline Both treatments showed a good efficacy in terms of reduction of HAMD-17 total score at V9 (56 days) compared to baseline (ITT: Trazodone OAD -12.9 ± 6.82, Venlafaxine XR -14.7 ± 6.56; PP: Trazodone OAD -15.4 ± 5.32, Venlafaxine XR -16.4 ± 5.39). Even if a statistically significant difference in favor of venlafaxine XR has been detected in the ITT population, while no difference was detected in the PP population, the primary endpoint of the trial, the non-inferiority of trazodone OAD compared to venlafaxine XR, has been met. The extent of the clinical relevance of this difference could be matter of debate and it probably warrants further studies. Moreover, the severity of disease in the treated population in both arms decreased from moderate to mild based on the HAMD-17 total score at visit 9 (56 days) (ITT: Trazodone OAD 10.8 ± 6.49, Venlafaxine XR 9.1 ± 6.00; PP: Trazodone OAD 8.5 ± 4.97, Venlafaxine XR 7.7 ± 5.07). An interesting result of this trial was the higher reduction of HAMD-17 score in the trazodone OAD group compared to the venlafaxine XR group at V3, after only 7 days of treatment. This difference was statistically significant ($p<0.05$). The results related to the mean HAMD-17 subscale sleep disturbance scores showed a statistically significant difference in favor of the trazodone OAD group compared to the venlafaxine XR group in the PP population at V3 (7 days), V4 (21 days), V6 (35 days), and V9 (56 days). As for the ITT population a statistically significant difference in favor of trazodone has been detected at V3 (7 days), V4 (21 days), and V6 (35 days). As for the anxiety/somatization scores of the HAMD-17, a statistically significant difference in favour of venlafaxine XR has been detected on V6 (35 days) and V9 (56 days) in the ITT population, and on V9 (56 days) in the PP population. As for the retardation scores of the HAMD-17, a statistically significant difference in favour of venlafaxine XR has been detected on V4 (21 days), V6 (35 days) and V9 (56 days) in the ITT population, and on V6 (35 days) and V9 (56 days) in the PP population. Regarding the cognitive disturbance scores of the HAMD-17, no significant difference has been reported between the two treatments.

The secondary endpoints included the change in the MADRS score from baseline, the distribution and change of CGI-S and CGI-G from baseline, and the rate of responders and remitters.The change of MADRS total score at V9 (56 days) from baseline was statistically significant for venlafaxine XR as compared to trazodone OAD both in the ITT and PP populations (ITT: Trazodone OAD -14.4 ± 7.65, Venlafaxine XR -16.9 ± 7.65 $p=0.003$; PP: Trazodone OAD -17.1 ± 6.01, Venlafaxine XR -18.6 ± 6.58 $p=0.016$). This result confirmed the difference already detected with the primary outcome measure, the change of the HAMD-17 total score at V9 (56 days) from baseline in the ITT population.

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Efficacy results: As for the change in the CGI-S score from baseline, a statistically significant difference was found in favor of venlafaxine XR as compared to trazodone OAD at V9 (56 days), in the ITT (trazodone OAD -1.8±1.16, venlafaxine XR 2.1±1.17, p=0.032), but not in the PP (trazodone OAD –2.1±1.06, venlafaxine XR -2.3±1.02, p=0.056) population. Regarding the CGI-G score from baseline, a statistically significant difference was detected in favor of venlafaxine XR as compared to trazodone OAD at V9 (56 days), both in the ITT (trazodone OAD 2.0±1.12, venlafaxine XR 1.7±0.99, p=0.0068) and PP (trazodone OAD 1.7 ± 0.82, venlafaxine XR 1.5 ± 0.72, p=0.0383) population. Moreover, the rate of responders, defined as a reduction of at least 50% of the HAMD-17 total score at V9 compared to the baseline score, in the present trial was reached in 65.4% of the subjects in the trazodone OAD group and 76.3% of the subjects in the venlafaxine XR group in the ITT population. As for the clinical remission, defined as a HAMD-17 score ≤ 7 at Visit 9, the present trial reported the following rates: ITT: Trazodone OAD 37.7%, Venlafaxine XR 52%; PP: Trazodone OAD 46%, Venlafaxine XR 60.6%.

Safety results: Three hundred twenty one patients (165 in the trazodone OAD group and 156 in the venlafaxine XR group) who took at least one dose of the study medication were included in the Safety population. Three hundred twenty two (322) AEs occurred in patients after initiation of the study treatment. One hundred sixty one occurred in 86 patients receiving trazodone OAD and 161 in 73 patients receiving venlafaxine XR. The most frequent AEs were: dizziness (11.18%) and somnolence (8.70%) in patients receiving trazodone OAD, and nausea (14.29%) and headache (11.80%) in patients receiving venlafaxine XR.Overall, the intensity of AEs experienced on both treatments was mild to moderate in majority of the cases. The AEs judged as severe occurred in 2 patients (2 AEs) in the trazodone OAD group and in 4 patients (7 AEs) in the venlafaxine XR group. More than 90% of the AEs resulted recovered/resolved and 254 AEs were judged by the Investigators as related (i.e., certain, probable/likely, possible) with the investigational medications: 121 occurred in 67 patients treated with trazodone OAD and 133 in 63 patients treated with venlafaxine XR. Five SAEs, including one death in venlafaxine XR group, occurred during the study and were experienced by 3 patients in trazodone OAD group and by 1 in venlafaxine XR group. Statistically significant differences between the two treatment groups were found in the changes of ECG parameters from the screening at post-randomizations visits. Particularly, at visit 9 the two groups were statistically significantly different in the changes from screening of QTcF, QT, RR and QRS. Eleven out of 165 patients in trazodone OAD group and 6 out of 156 patients in venlafaxine XR group showed QTcF values higher than 450 msec during the study or prolongation higher than 60 msec at any visit with respect to the screening value. These differences were probably due to the higher daily dose of trazodone OAD (median daily dose 300 mg) as compared to venlafaxine XR (median daily dose 75 mg). Anyway, this difference between the two treatment groups was not statistically significant. As expected, both treatments influenced ECG parameters, however across the study, no patients experienced ECG alteration judged as "abnormal and clinically significant". Statistically significant differences between the two treatment groups were found for the SBP, DBP and heart rate in the change from baseline at post-randomization visits. These differences were expected and not clinically significant.There were no notable changes in body weight and physical examination in either treatment group during the study.

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Conclusion: The aim of the study was to compare the antidepressant efficacy of trazodone OAD to venlafaxine XR. Consequently, one of the relevant goal of the enrolment was to provide investigators with new and solid data related to trazodone OAD as a valid therapeutic option to treat subjects affected by depression in clinical practice. In this study depressed patients administered with trazodone OAD were as likely to be successfully treated as patients administered with venlafaxine XR. Patients enrolled in this study were significantly ill, as measured by validated clinical inventories. Even if a statistically significant difference in favor of venlafaxine XR has been detected in the ITT population, while no difference was detected in the PP population, the primary endpoint of the trial, the non-inferiority of trazodone OAD compared to venlafaxine XR, has been met. The extent of the clinical relevance of this difference could be matter of debate and it probably warrants further studies. An interesting result of this trial was the higher reduction of HAMD-17 score in the trazodone OAD group compared to the venlafaxine XR group after only 7 days of treatment. This difference was statistically significant ($p<0.05$). Moreover, the rate of responders, in the present trial was 65.4% of the subjects in the trazodone OAD group and 76.3% of the subjects in the venlafaxine XR group in the ITT population. This rate was higher than the one reported in a previous study versus placebo carried out in 2009 by Sheehan et al., namely 54% of the subjects in the trazodone OAD group and 41.2% of the subjects in the placebo group in the ITT population. Furthermore, the response rate in the trazodone OAD group shown in the present trial is even higher than the one shown for citalopram (47% after 14 weeks of treatment) in the largest "real world" study on the treatment of nonpsychotic depression, the STAR*D trial. The overall efficacy of Trazodone OAD in this trial was even higher than the one shown in the study placebo by Sheehan et al. The trial by Sheehan et al. had the same study design as the present one and very similar population compared to the present one, thus allowing a reliable comparison of the results. Indeed, the mean reduction of HAMD-17 total score in the ITT population measured after 56 days of treatment in the trial conducted by Sheehan et al. was -11.4 ± 8.2, thus highlighting the consistency of the efficacy data produced by the present study and confirming once again the efficacy of trazodone OAD in treating depression. As for the clinical remission, at Visit 9, the present trial reported the following rates: ITT: Trazodone OAD 37.7%, Venlafaxine XR 52%; PP: Trazodone OAD 48%, Venlafaxine XR 60.6%. Once again, the remission rate of trazodone OAD group was higher than the one related to citalopram reported in the STAR*D trial (26% after 14 weeks of treatment). Considering the safety, 322 AEs occurred in patients after initiation of the study treatment: 161 experienced by 86 patients receiving trazodone OAD and 161 by 73 patients receiving venlafaxine XR. Overall, the intensity of AEs experienced on both treatments was mild to moderate in majority of the cases. More than 90% of the AEs resulted recovered/resolved and 254 AEs (121 trazodone OAD and 133 venlafaxine XR) were judged by the investigators as related with the investigational medications. Five SAEs, including one death in venlafaxine XR group, occurred during the study. As expected, both treatments influenced ECG parameters, however across the study, no patients reported ECG alteration judged as "abnormal and clinically significant". Taken all together these data could confirm the efficacy of trazodone OAD as a valid therapeutic option in the treatment of MDD. Both treatments showed a good safety and tolerability profile.

Date of the Clinical Report: 07July 2015