Supplementary Appendix: 1 Inclusion and Exclusion Criteria

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 the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM)-IV criteria as assessed using the Mini International Neuropsychiatric Interview; 4) 17-item HAM-D score ≥18 at both screening and baseline visits, together with a decrease not > 20% between screening and baseline; 5) symptoms of depression for at least 1 month before study entry (screening visit); 6) legally capable of giving their consent to participate in 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 time of signing the informed consent up to 30 days after the last administration of the investigational product.

Exclusion Criteria

Patients meeting the following criteria were excluded: 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 6 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 before the start of double-blind treatment; 8) positive present history of glaucoma; 9) history of risk

factors for Torsade de Pointes (e.g., heart failure, cardiac arrhythmias, bradycardia, cardiac conduction abnormalities, family history of long QT syndrome, cardiomyopathy, cardiac hypertrophy, chronic cardiac insufficiency); 10) values of electrolytes (sodium, calcium, potassium, magnesium, chloride) outside of the normal laboratory range and judged to be clinically relevant by the Investigator; 11) concomitant treatment with drugs known for QT prolongation, or with drugs producing hypokalaemia, or diuretics; 12) QTcF values higher than 450 msec in the electrocardiogram (ECG) performed at the screening; 13) history of major depression resistant to medical treatments (i.e., 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, with the exception of 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 (HAM-D, criterion 3 with a value $\geq$ 3); 18) presence of any primary psychiatric disorder other than major depression;19) history or presence of bipolar disorder, any psychotic disorder, or a mental disorder due to general medical conditions; 20) pregnancy, lactation, or a 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 2 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. An 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 1 month (3 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 the subject was the Investigator or his/her deputies, first grade relative, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the study.