«Exploring venlafaxine pharmacokinetic variability by a phenotyping approach »

MetAbolism vaRiability of VEnLafaxine: MARVEL

BIOMEDICAL RESEARCH PROTOCOL RELATING TO A MEDICINAL PRODUCT FOR HUMAN USE

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The research will be carried out in accordance with the protocol, with current good practices and with the legislative and regulatory provisions in force.

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The research received a favourable opinion from the CCP Ile de France I on 30 /09 /2015 and authorisation from the ANSM on 13 /10 /2015

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1. SUMMARY

Full title	«Exploring venlafaxine pharmacokinetic variability by a phenotyping approach »
Acronym	MARVEL
Coordinating Investigator	**Frank Bellivier** Department of Psychiatry Fernand Widal Hospital 200 rue du Faubourg Saint Denis 75475 Paris Cedex 10 Inserm UMR-S 1144 *Variabilité de Réponse aux Psychotropes* Universités Paris Descartes – Paris Diderot Tel. 01 40 05 42 01
Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	Regarding the direct costs and the social value of depression, the decision of an antidepressant treatment prescription must be optimized as much as possible. The development of a personalized medicine in psychiatry may reduce treatment failure, intolerance or resistance, and hence burden and costs of affective disorders. There is hope that biomarkers will be found to guide treatment selection. It might be of decisive interest to be able to assess an individual's metabolism activity. We propose here to explore the relationship between the activity of drug-metabolizing enzymes (DME) and transporters- assessed by a phenotypic approach and the efficacy of antidepressants. We will focus on venlafaxine (V) that provides a reasonable second-step choice for patients with depression and is used extensively in psychiatric practice, and the metabolism of which involves several cytochromes (CYP) P450 enzymes and the transporter P-gp.
Primary objective	To study the correlation between the concentration of V and its metabolite ODesmethylV (V+ODV) and drug metabolism variability assessed by a phenotypic approach.
Secondary objectives	To compare between responders and non responders, as well as between patients with or without side effects: - The CYP2C19 activity and the prevalence of each profile of metabolism - The CYP2D6 activity and the prevalence of each profile of metabolism - The CYP3A4 activity and the prevalence of of each profile of metabolism - The P-gp activity and the prevalance of each profile of transport To study the correlation between V+ODV concentration/dose and V+ODV concentration and antidepressant efficacy and tolerance

	To study the correlation between the ratio ODV/V and CYP2D6 activity To study the correlation between the concentration at 2 hours and the AUC (2,3,6 hours) of the metabolic ratio hydroxyomeprazole/omeprazole To conduct exploratory association analyses between blood biomarkers (candidate mRNA and miRNA) and the tolerance and efficacy of V To analyse the role of genetic variations of DNA in the determination of CYP2C19 and 2D6 phenotypes, in patients with PM profile.
Criteria of assessment	• (V+ODV) concentration • The CYP2C19 activity: 5-hydroxyomeprazole/omeprazole at 2 hours and $AUC_{2,3,6}$ of the Metabolic ratio 2, 3 and 6 hours after omeprazole oral administration • The CYP2D6 activity: dextrorphan/dextromethorphan ratio two hours after dextromethorphan oral administration • The CYP3A4 activity: 1-hydroxymidazolam/ midazolam ratio two hours after midazolam oral administration • The P-gp activity: Fexofenadine $AUC_{2,3,6}$ based on fexofenadine concentrations at 2, 3 and 6 hours after fexofenadine oral administration • Antidepressant efficacy: MADRS, HAMD, QIDS • Antidepressant tolerance: PRISE-M, FISBER • Antidepressant observance: MARS • Circulating mRNA and miRNA transcripts • Allelic variations: CYP2C19 **2*** and CYP2D6 **4* and 5***
Experimental design	Interventional Study (Recherche Bio-Médicale)
Population involved	Patient with major depressive disorder and MADRS ≥ 20 Despite 4 weeks of V regardless of the dose
Inclusion criteria	Patient (Hospitalized or outpatient) with major depressive disorder and MADRS ≥ 20 at visit of selection Patients non responders to V after 4 weeks of V regardless of the dose Decision of the psychiatrist to increase the dose of V at visit of selection Male and female Age ≥ 18 years Understanding of French language and able to give a written inform consent. Informed consent signed to participate to the study Individuals covered by social security regimen
Non-inclusion criteria	Patients treated by more than one antidepressant other than mirtazapine or mianserine Patients currently treated with one of the drug substrate of the cocktail and/or by esomeprazole Sensitivity or contra-indication to any of the substrate drugs used Current pregnancy, desire to get pregnant, or breastfeeding Bipolar disorder and schizophrenia

Background Therapy	Oral extended release Venlafaxine, regardless of the dose at selection, which will be increased up to 375mg during the study according to the psychiatric follow-up if necessary.
Challenge agents	For the assessment of drug-metabolizing enzyme activity, the patients **will be given the cocktail probe drugs, by oral route, one time during the study:** • A capsule of omeprazole 10mg • 6.8 ml of an oral liquid formulation of Dextrométhorphane bromhydrate (Tussidane 1.5mg/ml , syrup) • 1 mg of an injectable solution of Midazolam for oral administration (Midazolam 1mg/mL, injectable solution) • A tablet of fexofenadine 120mg
Other procedures added by the research	• The dosage of venlafaxine (V) and ODemethylV (ODV) • The collect of DNA, circulating, mRNA and miRNA transcripts • The assessment of drug efficacy, tolerance and adherence using standardized questionnaires
Risks added by the research	• The administration of a cocktail drugs with current authorization once during the study • Two blood samples of 5mL, one blood sample of 2.5ml, one blood sample of 7mL and three blood spots. Risque B
Practical procedure	The selection visit takes place during the usual medical follow-up and will include the measurement of a MADRS and HAMD score. The other visits will be carried out as part of a traditional hospitalization if it is needed regarding the patient's psychiatric condition. Conversely, they will be done during a day hospitalization (V0 and V1) or during a consultation (V2, V3). They will be systematically supervised by a practitionner. The inclusion (V0) takes place **0-20 days** after the increase in V dosage and will include: - Verification of inclusion and non inclusion criteria - Signature of the consent - Screen for tobacco use and Fagerstrom test - Characteristics of the mood disorder - Anxiety scale Tyrer - QIDS-SR16 - Criteria for rating medication trials for antidepressant failure and level of resistance - MARS score - PRISE-M score - FISBER score The visit V1 will take place between **7-21 days** after Visit V0 and will include: -Sampling for the dosage of venlafaxine (V) and ODemethylV (ODV)

	-The collect of DNA, circulating mRNA and miRNA transcripts -The phenotypic study The administration of the cocktail probe drugs: • A capsule of omeprazole 10mg • 6.8 ml of an oral liquid formulation of Dextrométhorphane bromhydrate (Tussidane 1.5mg/ml , syrup) • 1 mg of an injectable solution of Midazolam for oral administration (Midazolam 1mg/mL, injectable solution) • A tablet of fexofenadine 120mg The pill and liquid formulations will be taken orally successively with a glass of water. Followed by the Capillary blood samples at 2, 3 and 6 hours after the cocktail administration (1 drops each hour) from a small finger prick on the DBS device for the measurement of cocktail drug concentrations (drug parent and metabolites) The visits V2 and V3 will take place between **25-40 days (4 weeks)** and **50-70 days (8 weeks)** after Visit V0, with a psychologist or a doctor. They will included the assessment of drug efficacy, tolerance and adherence: - MARS score - PRISE-M score - FISBER score - MADRS - HAMD - QIDS-SR16
Number of subjects chosen	205
Number of centers	12 clinical centers in France 7 centers of clinical investigations in France 4 centers involved in biological analysis (3 in France and 1 in Switzerland)
Research period	The included subjects' length of participation: 7-70 days Inclusion period: 78 months Total maximal research period: 78 months+70 days=2442 days
Number of inclusions expected per center and per month	0.9/center/month
Statistical analysis	The statistical analysis will be performed once the sample size has been reached, and all the end point measures available. Our hypothesis is that the prevalence of patients with a CYP2C19 UM profile is twice as high in non-responders in comparison with responders, who have a CYP2C19 metabolic profile comparable to that of Caucasians (20%). To demonstrate that the prevalence is two-fold that observed in non-responders, with a type I error at 0.05 and a statistical power of 80%, the sample size is tabulated below according

	to the prevalence of response. Thus, to anticipate for potential large disproportion in responders/non responders (that will be only defined after study inclusion) we decided to include **205 patients**. This will allow to control for type I and type II error rates in the comparison of the prevalence of CYP2C19 UM profile among these groups. In addition the sample size will allow to study sufficient numbers of CYP2D6 PM, IM, and UM to determine the effects of CYP2D6 variations on V and ODV plasma levels and their efficacy or risk of adverse events. The type I error rate will be fixed at 0.05. All tests will be two-sided and compared thus to 0.05. Multiple imputations, which are a popular approach for handling the pervasive problem of missing data in biostatistics, will be used. It is usually performed under a missing at random (MAR) assumption. Multiple imputations by chained equation are to our knowledge the most flexible approach to handle complex patterns of missing data (including categorical data, quantitative data, and survival data). Primary analyses will be performed on an intent-to-treat basis. Secondary exploratory analyses will consider the population of compliers, that is, those who completed the treatment according to the scheduled protocol.
Funding source	PHRC AOM 14562 and for dosages for the determination of phenotypes: Department of pharmacology-toxicology, Geneva
Data Safety Monitoring Board anticipated	Non

1. SCIENTIFIC JUSTIFICATION FOR THE RESEARCH

1.1 Hypothesis for the research

Twenty to 45% of patients with major depressive disorder episode (MDE) in a psychiatric setting fail to achieve the goal of antidepressant agents[1,2]. As a consequence of consecutive failures, the concept of pseudoresistance and Treatment resistant depression (TRD) has emerged last years.

Regarding the direct costs and the social value of depression, the decision of an antidepressant treatment prescription must be optimized as much as possible. The development of a personalized medicine in psychiatry may reduce treatment failure, intolerance or resistance, and hence burden and costs of affective disorders.

There is hope that biomarkers will be found to guide treatment selection. It might be of decisive interest to be able to assess an individual's metabolism activity. We propose here to explore the relationship between the activity of drug-metabolizing enzymes (DME) and transporters assessed by a phenotypic approach and the concentration, efficacy and tolerance of antidepressants. We will focus on venlafaxine (V) that provides a reasonable second-step choice for patients with depression and is used extensively in psychiatric practice, and the metabolism of which involves several cytochromes P450 (CYP) enzymes and the transporter P-gp[3-5].

This naturalistic study will be able to give critical information about the reliability between the results of a phenotypic approach of drug metabolism and pharmacokinetics and pharmacodynamics of antidepressant (PD, i.e. efficacy and adverse events), before investigating the interest of a phenotypic-guided prescription approach study.

1.2 Description of knowledge relating to the pathology in question

1.2.1 Epidemiology and costs of depression

Depression is one of the most disabling diseases and is the fourth most disabling medical condition worldwide based on disability-adjusted life-years[6,7]. In 28 European countries with a population of 466 million, at least 21 million are affected by depression. This makes depression the most costly brain disorder in Europe, accounting for 33% of the total cost corresponding to 1% of the total economy of Europe[6]. In France, the cost of mental disorder has been recently estimated at Euro 109 billion in 2007, 20% of which are actual money spent and 80% the social value of disease consequences. Attributable indirect costs resulting from lost output due to permanent disability and suicide amounted Euro 24.4 billion and intangible costs from poor quality of life Euro 65.1 billion[8].

Part of the important costs is related to unpredictable response to antidepressant[9]. Resistance to treatment contributes to increase the costs of the disease. Patients with resistance to treatment are twice as likely to be hospitalized, have more outpatient visits, use more psychotropic medications, and have 19 times the depression-related costs compared to patients with depression that responds to treatment[10].

1.2.2 Therapeutic management of depression

Antidepressants are the first-line treatment for a MDE. They differ considerably in their side-effects profile, their metabolism, their potential for interacting with other drugs and in the danger they pose when taken in overdose. Second (e.g., bupropion, maprotiline, mianserin, trazodone) and third (e.g., selective serotonin reuptake inhibitors-SSRI, serotonin and

noradrenalinereuptake inhibitors-SNRIs, mirtazapine) generation ("newer") antidepressants are generally tolerated better than are the first generation ("older") tricyclic antidepressant agents (TCAs), and patients are, thus, less likely to discontinue them. Recent clinical practice guidelines have recommended that second-generation antidepressants, such as SSRI, should be considered among the best first-line options for the treatment of MDE, given their relative low toxicity and high tolerability[11].
Regarding differences in efficacy and tolerability between "newer" antidepressants, Cipriani et al. found in a meta-analysis of 117 randomized clinical trials with 25,928 patients that mirtazapine, escitalopram, V, and sertraline were significantly more efficacious than duloxetine, fluoxetine, fluvoxamine, paroxetine, and reboxetine[4].
At least 45% of patients with depressive episodes will not respond sufficiently to an adequately performed first-line treatment with any chosen antidepressant[3].
Remission rates with citalopram as the first step in STAR*D were 28 to 33 per cent, and response rates averaged 47 per cent[12]. After unsuccessful treatment with an SSRI, approximately one in four patients had a remission of symptoms after switching to another antidepressant[3]. Bupropion, sertraline or V provided a reasonable second-step choice for patients with depression[3].

1.2.3 Variability in drug metabolism

Cytochrome P450 (CYP) enzymes and drug influx and efflux proteins such as P-glycoprotein (P-gp) comprise the major DME system in humans and are important sources of pharmacokinetic and pharmacodynamic variability [13]. Genetic polymorphisms or environmental factors such as dietary components, toxins, or drugs can affect the activity of these enzymes and result in interindividual variations in drug concentrations.
Genetic factors have been largely studied. For a subset of genetic variations, the *in vivo* and *in vitro* studies have elucidated enzyme activities that are listed as increased, normal, decreased, absent or unknown. This list is available in *'The Human Cytochrome P450 (CYP) Allele Nomenclature Database'* (http://cypalleles.ki.se) that catalogues genetic variability in CYP enzymes. This information can be used, along with the number of functional allele and the presence of gene duplication, to predict the phenotypes of different CYP.
Poor or slow metabolizers (PM) have deficient metabolizing ability compared with persons with normal activity and increased drug parent concentrations are expected. Conversely, an increased amount of active metabolites in ultrarapid metabolizers (UM) are expected. Between these two extreme profiles, intermediate (IM) and extensive (EM) profiles are also described.

1.2.3.1 Variability in CYP2C19

CYP2C19 has been estimated to metabolize approximately 8% of common drugs and is involved in the metabolism of TCAs, SSRIs, anticonvulsants, monoamine oxydase inhibitors, benzodiazepines, proton pump inhibitors and platelet aggregation inhibitors amongst others[14]. CYP2C19 is highly polymorphic with at least 28 variant alleles of which many have no enzymatic activity. The variants *2-*8 have been shown to be inactive while CYP2C19*17 carriage confers some enhanced enzyme functionality. The distribution of CYP2C19 phenotypes is usually divided into PM and EM, according to the number of functional alleles. More recently, due to the discovery of an additional variant that confers an enhanced functionality, phenotypes have been designated as UM (two CYP2C19*17 alleles), EM (two functional alleles), IM (one functional/one dysfunctional) and PM (two dysfunctional alleles)[15]. The variant alleles and corresponding phenotypes distribute differently across racial/ethnic

groups. CYP2C19*17 is highly prevalent in Caucasians (~ 20%) with similar frequency in Africans (Ethiopians 18%, Ugandans 17%) but low frequency in Asian populations (Koreans 0.3%, Japanese 1% and Chinese 4%)[16]. PM phenotypes are more frequent in Asian populations. The prevalence of phenotypes metabolizers of CYP2C19 in Caucasians is reported in **Table 1**.

1.2.3.2 Variability in CYP2D6

CYP2D6 is responsible for the metabolism of approximately 20 to 25% of all marketed drugs and especially of the following drug classes: antipsychotics, SSRIs, TCAs, opiates and serotonin 5HT3 agonists. CYP2D6 is highly polymorphic with over 100 variant alleles and a series of sub-variants; the number of alleles is still growing[17]. The prevalence of phenotypes metabolizers in Caucasians is reported in **Table 1**. CYP2D6 duplication occurs in 1–3% of Caucasians in Northern Europe, while frequencies of 9% and 29% of individuals carrying CYP2D6 duplication have been reported in Ethiopians and Tanzanians[16].

Table 1: Prevalence of phenotypic subgroups in Caucasians

Phenotypes metabolizers	**Ultrarapid**	**Extensive**	**Intermediate**	**Poor**
CYP2D6 [18,19]	10%	48%	35%	7%
CYP2C19 [20,21]	20%	77%		3%

1.2.3.3 Variability in CYP3A4

Substrate probes for CYP3A family isoforms are often metabolized by both CYP3A4 and CYP3A5. Both enzymes metabolize approximately half of oral drugs currently marketed. It is well recognized that their activity in adults varies widely between individuals.

More than 30 single nucleotide polymorphisms (SNPs) have been identified in the CYP3A4 gene. The most common variant, CYP3A4*1B has an allele frequency ranging from 0% (Chinese and Japanese) to 45% (African-Americans)[16]. However, studies have not linked CYP3A4*1B with alterations in CYP3A substrate metabolism[22]. Moreover, unlike other human P450s, such as CYP2D6 or CYP2C19, there is no evidence of a 'null' allele for CYP3A4.

CYP3A5 is polymorphically expressed in adults with readily detectable expression in about 10-20% in Caucasians, 33% in Japanese and 55% in African-Americans[16]. CYP3A5*3 is the most common polymorphism present in all ethnic groups and causes the absence of a functional CYP3A5 protein. Its prevalence among racial/ethnic groups is about 30% in African Americans and 90% in Caucasians[16].

Thus, it has been suggested that the variability in activity has a genetic basis, but common polymorphisms in CYP3A4 and CYP3A5 do not appear to have important functional significance. Thus, the complex regulatory pathways, environmental factors, or undetermined genetic haplotypes, may confound evaluation of the effect of individual CYP3A genetic variations on drug disposition, efficacy and safety.

1.2.3.4 Variability in P-gp activity

P-glycoprotein (P-gp), encoded by the MDR1 (or ABCB1) gene, regulates the efflux of many drugs. The MDR1 gene is highly polymorphic with more than 100 sites with a minor allele frequency higher than 5%[23]. Polymorphisms in the MDR1 gene may have an impact on the expression and function of P-gp, thereby influencing the response to antidepressants, which are substrates of this protein at the BBB and in the intestine. Among MDR1 SNPs, many

researchers have focused on the C3435T synonymous variant. The distribution of the variant is significantly influenced by ethnicity[24]. Marked differences in genotype and allele frequency are apparent between African populations and Caucasian/Asian populations. While allelic frequency varies between 73 and 83% in African populations, the frequency is only between 34 and 59% in non-African population, with the minimal allelic frequency reported in the Southwest Asian population[25]. The plasma concentrations of fexofenadine, a specific P-gp substrate, after a single oral administration were lower in 2677AA/3435CC subjects than in subjects with the other 5 genotype combinations of the SNPs of G2677T/A and C3435T[26].

1.2.3.5 Phenotypic approach of drug metabolism

1.2.3.5.1 Principles of the method

The pharmacokinetic variability and modifications in activities of CYP and/or P-gp can cause various pharmacological and toxicological consequences. It is therefore important to precisely and reliably evaluate their *in vivo* activity.

Besides the therapeutic drug monitoring that allows quantification of circulating drug concentration in an individual during a treatment, and genotyping tests for common variants of drug metabolism genes, a more efficient approach may be used to assess the activity of the enzymes involved in drug metabolism and transport, independently of a specific treatment or even before starting it [27-31].

Phenotyping consists of the administration of probe substances metabolized by a specific cytochrome or transported by P-gp for example, followed by the determination of a metabolic ratio or the evaluation of the plasmatic or urinary concentrations of the probes. The major strength of this approach is the direct measure of drug metabolism. Indeed, alternative approaches based on gene polymorphism identification do not provide an accurate estimate because of poor genotype / phenotype correlation for some genes. In addition, for different enzymes or transporters, no common variant associated with phenotype has been observed[29].

The administration of a cocktail containing several probe substrates allows the simultaneous evaluation of the activity of several cytochromes and P-gp in a single test, avoiding the influence of variability over time on phenotyping results.

Several cocktails have been developed and used over the past years (**Table 2**). However, these cocktails have several limitations, thus limiting their use in clinical settings. Some of the probe drugs used in many cocktails such as tolbutamide, mephenytoin or debrisoquine, are no longer available as marketed drugs in most countries. Moreover, only very few include P-gp probes. Another limitation is the use of therapeutic doses or insufficiently validated probes which might provoke side effects[32] especially if used in clinical practice facing a more vulnerable population. This limitation may be overcome by the use of lower probe doses but requires the development of sensitive analytical methods. Several currently available phenotyping procedures require tedious and multiple venous blood sampling[33,34]. For few cocktails, limited sampling strategies and phenotyping indices have been proposed, but these cocktails require the collection of both plasma and urine samples[35-37].

Table 2: Examples of phenotyping cocktails

Cocktail	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4	P-gp
GW cocktail[38]	caffeine	diclofenac	mephenytoin	debrisoquine	midazolam	/
Karolinska[35]	caffeine	losartan	omeprazole	debrisoquine	quinine	/
Cooperstown[33]	caffeine	warfarin	omeprazole	dextromethorphan	midazolam	/
Clement et al.[39]	caffeine	flurbiprofen	omeprazole	dextromethorphan	midazolam	/
Pittsburgh[37]	caffeine	flurbiprofen	mephenytoin	debrisoquine	/	/
Inje[36]	caffeine	losartan	omeprazole	dextromethorphan	midazolam	/
Turpault et al.[34]	caffeine	warfarin	omeprazole	metoprolol	midazolam	/
Videau et al.[40]	caffeine	tolbutamide	omeprazole	dextromethorphan	midazolam	digoxin
Croft et al.[41]	caffeine	tolbutamide	/	/	midazolam	fexofenadine

1.2.3.5.2 The Geneva Cocktail

A novel and promising approach for CYP and P-gp activity phenotyping is the use of dried blood spots (DBS) as a sampling procedure. This sampling method has been successfully applied for both therapeutic drug monitoring and pharmacokinetic studies[42-44].

The team of Prof Dayer, in Geneva, has recently evaluate the usefulness and effectiveness of DBS sampling for simultaneous assessment of the activities of six CYP isoforms and P-gp using a low dose phenotyping cocktail composed of caffeine (CYP1A2), bupropion (CYP2B6), flurbiprofen (CYP2C9), omeprazole (CYP2C19), dextromethorphan (CYP2D6), midazolam (CYP3A), and fexofenadine (P-gp).

The reliability of the method for the assessment of the modulation of CYP and P-gp activities was examined both by administration of the cocktail alone and in the presence of known CYP and P-gp inhibitor and an inducer. This can be seen by the modification of the fexofenadine AUC (**Figure 1**) or the metabolic ratios of the probes (**Figure 2**) when the cocktail is co-administered with CYP or P-gp inhibitor or inducer.

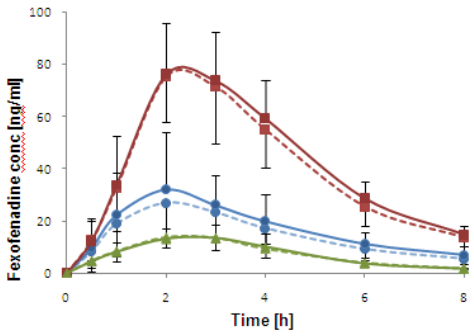

Figure 1: Concentration-time profile of fexofenadine in capillary DBS (dashed lines) and venous plasma samples (continuous lines) after administration of the cocktail capsule alone (circles), with P-gp inhibitor (squares) or with P-gp inducer (triangles)

They studied the Spearman rank correlation coefficients (ρ_s) between the Metabolic ratio (MR) at each time point and the AUC_{last} ratios for each session (**Table 3**). Limited (three- or four-point) sampling strategy was evaluated for P-gp activity assessment, and the best correlation ($\rho_s \geq 0.96$; $P < 0.001$) for each session was observed between AUC_{last} and $AUC_{2,3,6}$. Limited $AUC_{2,3,6}$ sampling perfectly predicted the magnitude of interactions, as shown by the mean 3.0-fold $AUC_{2,3,6}$ (vs. 2.8-fold for AUC_{last}) increase after quinidine administration and 48% $AUC_{2,3,6}$ (vs. 45% for AUC_{last}) decrease after rifampicin pretreatment in the DBS method.

The MRs for cafeine (0.5–8h), bupropion (1–8h), flurbiprofen (2–8h), and dextromethorphan (1–8h) were highly correlated with their respective AUC_{last} ratios at each separate session ($\rho_s > 0.74$; $P < 0.015$). For midazolam, MRs at 0.5, 1, and 2 h of each session significantly correlated with the AUC_{last} ratio ($\rho_s > 0.64$; $P \leq 0.043$). For omeprazole, the correlation was significant at 2, 3, and 4 h of the cocktail-alone session and at the inhibition session ($\rho_s > 0.69$; $P \leq 0.025$), but no correlation was observed at the induction session (**Table 3 and 3 bis**).

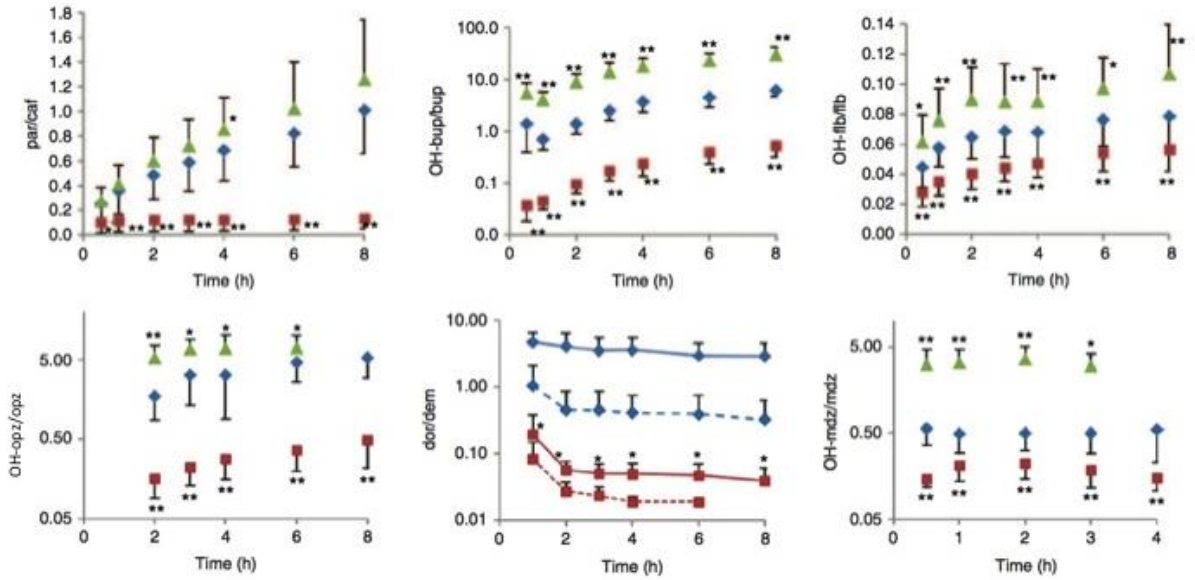

Figure 2: Metabolic ratio profiles after oral administration of cocktail capsule alone (diamonds), with inhibitor (squares) or with inducer (triangles) in dried blood spots. *p<0.05; **p<0.01; ***p<0.001. bup, bupropion; CAF, caffeine ; DEM, dextromethorphan ; DOR, dextrorphan; mdz, midazolam; OH-bup, 4-hydroxybupropion; OH-flb, 4-hydroxyflurbiprofen; flb, flurbiprofen; OH-mdz, 1-hydroxymidazolam;OH-opz, 5-hydroxyomeprazole; opz, omeprazole; PAR, paraxanthine

Sampling points used for AUC determination (h)	Cocktail alone		Cocktail + inhibitor(s)		Cocktail + inducer	
	ρ_s	*P* value	ρ_s	*P* value	ρ_s	*P* value
1, 2, 4	0.952	<0.001	0.685	0.029	0.842	0.002
2, 3, 4	0.976	<0.001	0.806	0.005	0.939	<0.001
2, 3, 6	**0.976**	**<0.001**	**0.964**	**<0.001**	**0.964**	**<0.001**
2, 4, 6	0.976	<0.001	0.915	<0.001	1.000	<0.001
1, 2, 4, 6	0.988	<0.001	0.939	<0.001	1.000	<0.001

Chosen limited-sampling AUC is shown in bold.

AUC, area under the plasma concentration–time curve; DBS, dried blood spot.

Table 3: Spearman rank correlations (ρ_S) between fexofenadine AUC_{0-8} and different three- or four-point fexofenadine AUCs in DBS at different sessions

Table 3 bis: Spearman rank correlations (ρ_S) between the AUC_{last} ratios of metabolite/probe and the metabolic ratios in DBS at various time points at different sessions

			Cocktail alone		Cocktail + inhibitor(s)		Cocktail + inducer	
CYP	Phenotyping indexes	Sampling time (h)	ρ_s	*P* value	ρ_s	*P* value	ρ_s	*P* value
2C19	[OH-opz]/[opz]	2	0.809	0.005	0.869	0.001	0.285	0.425
		3	0.806	0.005	0.867	0.001	0.479	0.162
		4	0.697	0.025	0.888	0.001	0.418	0.229
		6	0.612	0.060	0.891	0.001	0.750	0.052
		8	0.511	0.132	0.924	<0.001	0.200	0.747
	$\frac{AUC_{2,3,6\ OH\text{-}opz}}{AUC_{2,3,6\ opz}}$	**2, 3, 6**	**0.855**	**0.002**	**0.964**	**<0.001**	**0.855**	**0.002**
2D6	dor/dem	1	0.891	<0.001	0.745	0.013	—	—
		2	1.000	<0.001	0.948	<0.001	—	—
		3	**1.000**	**<0.001**	**0.964**	**<0.001**	—	—
		4	0.988	<0.001	0.979	<0.001	—	—
		6	0.976	<0.001	0.918	<0.001	—	—
		8	0.976	<0.001	0.821	0.023	—	—
3A4	[OH-mdz]/[mdz]	0.5	0.830	0.003	0.862	0.001	0.697	0.025
		1	0.915	<0.001	0.760	0.011	0.647	0.043
		2	**0.745**	**0.013**	**0.742**	**0.014**	**0.673**	**0.033**
		3	0.745	0.013	0.762	0.010	0.500	0.391
		4	0.442	0.200	0.738	0.015	—	—
		6	0.895	0.001	0.911	<0.001	—	—

Advantages of the Geneva Cocktail Phenotypic approach

Direct and simultaneous measure of different cytochromes and transporter P-gp

Simultaneous determination in a single test, avoiding the influence of variability over time on phenotyping results

Low dose substrates

Limited sampling strategy

Metabolic ratio at 2 hours highly correlated with AUC $ratio_{0\text{-}8h}$ for each CYP probes and fexofenadine AUC $_{2,3,6h}$

Analytical method developed on Dried blood spot analysis

1.2.3.6 Investigating DNA variations, messenger RNA (mRNA) and micro RNA (miRNA) as biomarkers of metabolism or response

In this project, we will collect informations on Venlafaxine metabolism as well as therapeutic/side-effect response to Venlafaxine. The primary objective of this project is to test the influence of CYP metabolism on the variance observed on these variables.

CYP metabolism is partly genetically determinated and genetic variations can determine for CYP poor metabolizer profile, as well as can drug-drug interactions. Then, we want to have the chance to explore genetic variations in case of abnormal metabolic status to understand the part of them that are genetically determinated or not.

Other mechanisms are likely to contribute to inter-individual variability in metabolism and response. Therefore, we want to conduct exploratory analyses testing candidate mRNA in association with therapeutic response, side-effects and metabolism. Candidate genes will be selected according to preliminary data obtained in our network of research and recently

published data[45]. Other biomarkers of interest include circulating miRNA as they are likely to better reflect brain changes following Venlafaxine prescription.
These exploratory approaches may lead to the identification of biomarkers associated witha the efficacy and safety of therapeutics. Moreover, comprehensive cataloging of cell-free circulating RNAs may open a window to assess drug-associated adverse effects at the systems level [46].

1.3 Summary of relevant pre-clinical experiments and clinical trials

1.3.1 Antidepressant and Drug-metabolizing enzymes variability

Different studies showed that genetic variations of CYP2C19 or CYP2D6 are associated with drug concentrations, tolerance and efficacy of antidepressive agents[47-50]. The first dose recommendations based on genotype/phenotype of CYP2D6 were developed in 2001[51]. More recently, "Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association", on the basis of an exhaustive review of the literature focusing on amitriptyline, has also developed dosing recommendations for TCAs, in accordance with the predicted-phenotype of CYP2D6 and CYP2C19[52]. Hall-Flavin et al. evaluated the potential benefit of an integrated, five-gene pharmacogenomic test and interpretive report (GeneSight) for the management of psychotropic medications used to treat major depression in an outpatient psychiatric practice. They demonstrated an improvement in depression outcomes in using this tool[53].
Different ABCB1 polymorphisms also influence the disposition of antidepressant in plasma and cerebrospinal fluid (CSF) under steady-state conditions and this knowledge influences remission rates and depression scores[54,55].
However, at this time, there is not enough evidence or no reliable basis to justify routine genotyping for patients with depression. Pharmacogenetic testing for genetic variants of metabolizing enzymes may be considered for patients who do not respond to pharmacotherapy.
The major strength of phenotyping is the direct measure of drug metabolism. Actually, poor genotype / phenotype correlations exist for some genes. In addition, for different enzymes or transporters, no common variant associated with phenotype has been observed[29]. To date, phenotyping in clinical practive has not been yet evaluated and is a promising approach of metabolism variability and may be easily used in clinical practice.

1.3.2 Venlafaxine, a second step choice with high interindividual variability

1.3.2.1 The benefit of venlafaxine

In a clinical prospective study conducted in adult outpatients with a nonpsychotic MDD, who had no remission of symptoms or could not tolerate the SSRI citalopram, remission rates were 21-25 per cent for sustained-release bupropion, 17-27 per cent for sertraline, and 25 per cent for V-XR. Response rates were 26.1 per cent for sustained-release bupropion, 26.7 per cent for sertraline, and 28.2 per cent for V-XR. These treatments did not differ significantly with respect to outcomes, tolerability, or adverse events[3].
In a study where 149 patients with treatment resistant depression were included with a minimum score of MADRS at 20, response (defined as a 50% reduction in MADRS scores) was effective in 69% of patients after 8 weeks of treatment in the initial study phase, and

73% were responders at their final extension-phase visit (up to 10 months)[56]. The patients maintained their response for up to 10 months after an 8-week phase of treatment and showed some evidence of further improvement.
Regarding differences in efficacy and tolerability between “newer” antidepressants, Cipriani et al. found in a meta-analysis of 117 randomized clinical trials with 25,928 patients that mirtazapine, escitalopram, V, and sertraline were significantly more efficacious than duloxetine, fluoxetine, fluvoxamine, paroxetine, and reboxetine[4].
Then, V provides a reasonable second-step choice for patients with depression and is used extensively in psychiatric practice[3,4].

1.3.2.2 Pharmacodynamic properties

The mechanism of V's antidepressant action in humans is believed to be associated with its potentiation of neurotransmitter activity in the central nervous system (CNS). Preclinical studies have shown that V and its major metabolite, ODV, are inhibitors of serotonin and noradrenaline reuptake. V also weakly inhibits dopamine uptake. V and its active metabolite reduce β-adrenergic responsiveness after both acute (single dose) and chronic administration. V and ODV are very similar with respect to their overall action on neurotransmitter reuptake and receptor binding. V has virtually no affinity for rat brain muscarinic, cholinergic, H-histaminergic or alpha-adrenergic receptors in vitro.
Pharmacological activity at these receptors may be related to various side effects seen with other antidepressant medicinal products, such as anticholinergic, sedative and cardiovascular side effects. V does not possess monoamine oxidase (MAO) inhibitory activity. *In vitro* studies revealed that V has virtually no affinity for opiate or benzodiazepine sensitive receptors.

1.3.2.3 Venlafaxine pharmacokinetic properties

V is extensively metabolised, primarily to the active metabolite ODV. Mean ± SD plasma half-lives of V and ODV are 5±2 hours and 11±2 hours, respectively. Steady-state concentrations of V and ODV are attained within 3 days of oral multiple-dose therapy. V and ODV exhibit linear kinetics over the dose range of 75 mg to 450 mg/day [57].
At least 92% of V is absorbed following single oral doses of immediate-release V. Absolute bioavailability is 40% to 45% due to presystemic metabolism. After immediate-release V administration, the peak plasma concentrations of V and ODV occur in 2 and 3 hours, respectively. Following the administration of V prolonged-release capsules, peak plasma concentrations of V and ODV are attained within 5.5 hours and 9 hours, respectively. When equal daily doses of V are administered as either an immediate-release tablet or prolonged-release capsule, the prolonged-release capsule provides a slower rate of absorption, but the same extent of absorption compared with the immediate-release tablet. Food does not affect the bioavailability of V and ODV.
V and ODV are minimally bound at therapeutic concentrations to human plasma proteins (27% and 30%, respectively). The volume of distribution for V at steady-state is 4.4±1.6 L/kg following intravenous administration.

1.3.2.4 The variability of venlafaxine metabolism

A standard dose of the V will not have similar expected effects in all patients. This is partly explained by its PK that shows a high degree of inter-individual variability, related to variability in drug metabolism[58,59] (**Table 4**).

Table 4: Venlafaxine pharmacokinetic variability

Drug and dose range	Cmax (ng/ml)	Tmax or peak plasma level (h)	AUC 0-24 or 0-inf (ng.h/ml)	Elimination half life (h)
2x75mgXR SOD	107±42(p) 163±53(met)	6.1±1.5 (p) 10.5±3.0(met)	1587±1206(p) 4132±1491(met)	11.8±6.9(p) 13.2±3(met)
1x50mg IR SOD	82±28(p) 120±30(met)	3.0±1.4 (p) 5.5±3.4(met)	571±442(p) 1558±465(met)	5.0±3.2(p) 9.6±2.5(met)

Figure 3 displays the metabolism of V. V is highly metabolized in humans, with an urinary excretion of the unchanged compound between 1 and 10%. CYP2D6 appeared to be the dominant enzyme with the highest intrinsic clearance[60,61]. It is even considered that the metabolic ratio ODV/V is a marker of CYP2D6 activity[62,63]. Fogelman et al. also implicated CYP2C19, CYP2C9, and CYP3A4 in the metabolism of V to N-desmethyl V with the highest intrinsic clearance being attributable to CYP2C19[5]. Whereas CYP3A4 intrinsic clearance is lower than CYP2C19, the high in vivo abundance of 3A isoforms is thought to magnify the importance of this cytochrome. N,O-didesmethyl V is formed by continued metabolism of N-desmethyl V and ODV by CYP2C19 and CYP2D6[64,65]. Moreover, as V is a weak inhibitor of CYP2D6 and CYP3A4, CYP2C19 pathways are though to be significantly involved in ODV metabolism[66].

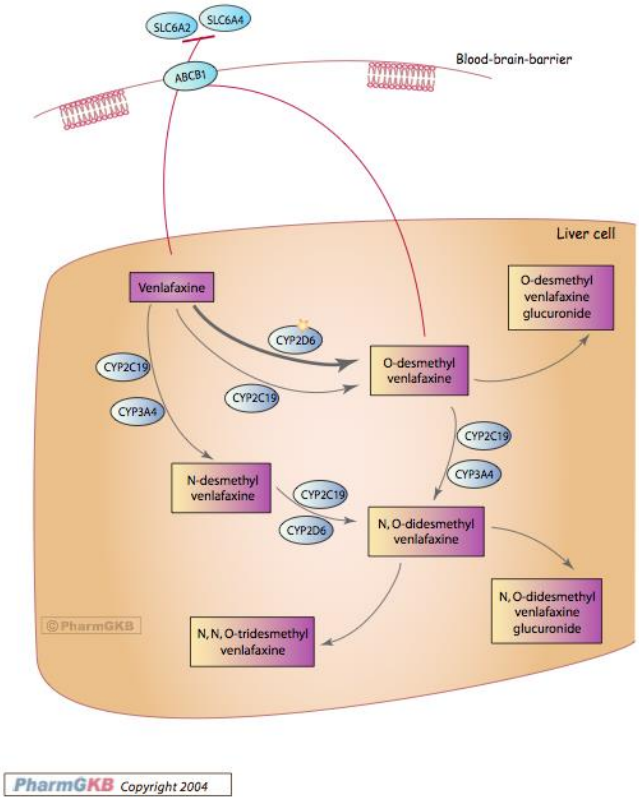

Figure 3: Metabolism of venlafaxine

The metabolite ODV is considered to have serotonin and norepinephrine reuptake inhibitor activity[57]. Clearly, the administered drug dose influences serum concentration of V, but as both V and ODV are pharmacologically active, the actual serum concentrations of both compounds achieved during treatment are likely to have clinical significance. However, the sum of serum concentrations of V and ODV does not differ significantly among groups with

two, one, or no functional CYP2D6 alleles[67].

Only a few small studies (n=25–464) and case reports have investigated the effect of CYP2D6 variants on V response or the risk of adverse reaction during V treatment.

One study used V as a phenotyping probe to classify PM and extensive metabolizer (EM) also found an influence on VEN treatment efficacy [68]. This study represented a secondary analysis of the V and ODV plasma levels from the four double-blind, placebo-controlled trials that were part of the V approval process. The results show that V is more effective than placebo in CYP2D6 EM but not in CYP2D6 PM. The discontinuation rate, side-effect rate, and V dose were not different between PM and EM. An earlier study in a smaller cohort (n = 33) showed that response was associated with a higher ODV/V ratio among EM [69]. The study only included three PM and two UM patients and could not establish a relationship between higher V concentration and an increased likelihood of side effects or treatment response. In contrast, other studies have not been able to link V response with ODV and V plasma levels or the CYP2D6 genotype significant[61,70-72]. An accompanying editorial proposes that CYP2D6 PM patients are less responsive to V because CYP2D6 has pharmacodynamics effects on the metabolism of serotonin in the brain[73].

The effect of CYP2C19 in V metabolism is not well understood. As both PM and UM variations of CYP2C19 are present in most populations, it is reasonable to expect that these may have an impact on V metabolism. Some studies have indicated that polymorphisms in both CYP2D6 and CYP2C19 correlated with interindividual differences in the PK of V and might therefore impact serum V and ODV concentrations as well[71,74,75]. Moreover the combined missing CYP2D6 and CYP2C19 activity has been involved in the occurrence of a fatal drug poisoning case in a patient receiving venlafaxine[76]. McAlpine et al. showed a significant positive effect of both CYP2D6 and CYP2C19 genotype scores on ODV/V ratio (CYP2D6: r =0.44,p=0.001; CYP2C19: r=0.26, p=0.009), consistent with the hypothesis that both enzymes are involved in V metabolism. The highest ODV/V ratios were related to highest CYP2D6 activity. However, they also demonstrate that CYP2D6 and CYP2C19 allelic variants are independent predictors of lower total concentration (CYP2D6: P=0.021, CYP2C19: P=0.001). Figure 4 shows the relationship between V plus ODV and CYP2C19 genotypes for subjects taking low (less than 225 mg) and high doses (225 mg or greater).

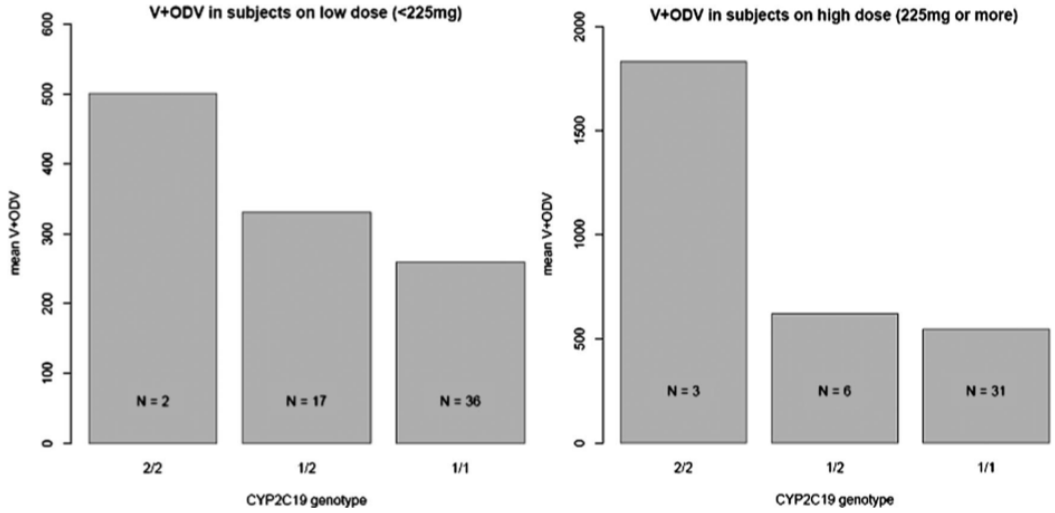

Figure 4: Relationship between total concentration of (V+ ODV) and CYP2C19 genotypes. The black bars represent 95% confidence interval for mean V + ODV in each group. CYP2C19 genotypes *2/*2, *2/*1, and *1/*1, correspond to activity scores of 0, 1, and 2, respectively.

Hence, it is recognized that variations in both CYP2D6 and CYP2C19 genes determine V+ODV pharmacokinetic. This variability may have important clinical consequences such as unpredictable response and/or adverse drug reactions at therapeutic doses.
The inclusion of the CYP2C19 variability may help to understand the variability in V response. Larger studies are also needed to study sufficient numbers of PM and UM to determine whether the effect of CYP2D6 and CYP2C19 variations on V and ODV plasma levels translates into an increased risk for nonresponse and side effects.
Furthermore, to the best of our knowledge no study has investigated the effect of variations in CYP2C19 activity on V concentration, efficacy and tolerance.

1.3.2.5 Venlafaxine prescription

The recommended starting dose for prolonged-release V is 75 mg given once daily. Patients not responding to the initial 75 mg/day dose may benefit from dose increases up to a maximum dose of 375 mg/day. Dosage increases can be made at intervals of 2 weeks or more. If clinically warranted due to symptom severity, dose increases can be made at more frequent intervals, but not less than 4 days.
Because of the risk of dose-related adverse effects, dose increments should be made only after a clinical evaluation. The lowest effective dose should be maintained.
The antidepressant V is prescribed in accordance with

- The recommendations
- The psychiatric status of the patient
- The habits of the psychiatrist
- At the posology decided by the psychiatrist
- Blinded regarding the results of the phenotypic study.
- The respect of contra indications

Patients should be treated for a sufficient period of time, usually several months or longer. Treatment should be reassessed regularly on a case-by-case basis. Longer-term treatment may also be appropriate for prevention of recurrence of major depressive episodes (MDE). In most of the cases, the recommended dose in prevention of recurrence of MDE is the same as the one used during the current episode.
Antidepressive medicinal products should continue for at least six months following remission.

1.3.2.6 Venlafaxine Undesirable effects

V is well tolerated, being associated with fewer anticholinergic and Central nervous system adverse effects than tricyclic antidepressants. Unlike the tricyclic antidepressants, V does not appear to significantly affect cardiac conduction, although there have been a few reports of modest increases in blood pressure, particularly after high doses of the drug. These advantages may include a rapid onset of action and reduced propensity to cause anticholinergic effects and cardio toxicity compared with tricyclic antidepressants.
The most commonly (>1/10) reported adverse reactions in clinical studies were nausea, dry mouth, headache and sweating (including night sweats).

Resistance to treatment contributes to increase the costs of depression. Patients with resistance to treatment are twice as likely to be hospitalized, have more outpatient visits, use more psychotropic medications, and have 19 times the depression-related costs compared to patients with depressions that respond to treatment.
Several recent studies have highlighted the interest of determining DME variability in the management of depressive patients. They mainly focused on genetic approach of DME activity.
It is recognized that variations in both CYP2D6 and CYP2C19 genes determine venlafaxine+ODV pharmacokinetics. Only a few small studies and case reports have investigated the effect of CYP2D6 variants on V response or the risk of adverse reaction, while no study has investigated the effect of variations in CYP2C19 activity on V efficacy and tolerance.
To date, large studies with sufficient numbers of CYP2C19 and CYP2D6 PM and UM are needed to determine whether the effect of these CYP affect V tolerance and efficacy.
Phenotypic approach is an efficient approach of the activity of phase I enzyme and Pgp transporter. Novel and promising methods have been developped and may be helpful in diseases with therapeutic challenge.

1.4 Description of the population to be studied and justification for the choice of participants

We will focus on patients with severe major depressive episode (MDE)

1.4.1 Definition of Major Depressive episode and disorder (DSM-V)

A MDE is not a disorder in itself, but rather is a description of part of a disorder, most often major depressive disorder (MDD) or bipolar disorder.
A person who suffers from a MDE must either have a depressed mood or a loss of interest or pleasure in daily activities consistently for at least a 2 weeks period. This mood must represent a change from the person's normal mood; social, occupational, educational or other important functioning must also be negatively impaired by the change in mood.
A MDE is also characterized by the presence of 5 or more of these symptoms:

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feeling sad or empty) or observation made by others (e.g., appears tearful). (In children and adolescents, this may be characterized as an irritable mood.)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
4. Insomnia (inability to sleep) or hypersomnia (sleeping too much) nearly every day
5. Psychomotor agitation or retardation nearly every day
6. Fatigue or loss of energy nearly every day
7. Feelings of worthlessness or excessive or inappropriate guilt nearly every day
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

Montgomery and Asberg Depression Rating Scale

The Montgomery–Åsberg Depression Rating Scale (abbreviated MADRS) is a ten-item diagnostic questionnaire which psychiatrists use to measure the severity of depressive episodes in patients with mood disorders[77]. It was designed in 1979 by British and Swedish researchers as an adjunct to the Hamilton Rating Scale for Depression (HAMD), which would be more sensitive to the changes brought on by antidepressants and other forms of treatment than the Hamilton Scale was. There is, however, a high degree of statistical correlation between scores on the two measures.

Each item is coted 0 to 6 by the physician. The maximal score is 60. Depression is defined by a score ≥ 15. Its severity is defined by a score >30. MADRS remission is defined by a score < 9 [78].

1.5 Identification and description of the experimental and non experimental medication

1.5.1 Venlafaxine (experimental medication)

V provides a reasonable second-step choice for patients with depression and is used extensively in psychiatric practice[3,4]. V is a phenylethylamine derivative, which, together with its major metabolite, facilitates neurotransmission in the brain by blocking presynaptic reuptake of serotonin (5-hydroxytryptamine: 5-HT) and noradrenaline (norepinephrine)[57]. The clinical studies investigating V efficacy in patients with MDE, its pharmacokinetic and pharmacodyamic properties has been detailed in the paragraph 1.3.2. Description and justification of the dosage, administration method, administration design and treatment period are given in paragraph 1.6.

1.5.2 The assessment of DME activity: the use of probes substrates (non experimental medication)

Several drugs will be administered during the study, in different indications than those for which they have been marketed, in order to assess the activity of 3 CYP and one transporter. Additional details about theses drugs are given in paragraph 6.

1.5.2.1 Omeprazole, a proton pump inhibitor, 10mg

The activity of CYP2C19 can be assessed by the administration of omeprazole, substance that is selectively metabolised by this cytochrome to the inactive metabolite, 5-hydroxyomeprazole[79-81].

1.5.2.2 Dextromethorphan, an opioid antitussive drug, 10mg

Dextromethorphan is specifically metabolised to an active metabolite - dextrophan by CYP2D6[82,83].

1.5.2.3 Midazolam, a benzodiazepine, 1mg

CYP3A4 and CYP3A5 have the same substrate specificity. It is difficult to estimate the individual contribution of these respective isoenzymes in drug metabolism. Therefore, the probe substrates estimate generally the activity of the CYP3A subfamily without distinguishing between the isoenzymes. Midazolam is selectively and almost entirely

metabolised to 1-hydroxymidazolam (and to a smaller extent 4-hydroxy- and 1,4-hydroxymidazolam) [84]. This reaction is catalysed by both CYP3A4 and CYP3A5. Unlike many others CYP3A metabolised drugs, midazolam is not a P-gp substrate an important characteristic when specific probe is needed.

1.5.2.4 Fexofenadine, a non sedating histamine H1 receptor agonist 120mg

Fexofenadine is not metabolized by any CYP and is a P-gp substrate used as probe for the evaluation of P-gp activity[85,86].

1.6 Description and justification of the dosage, administration method, administration design and treatment period.

1.6.1.1 Venlafaxine

The antidepressant V will be prescribed in accordance with

- The recommendations
- The psychiatric status of the patient
- The habits of the psychiatrist
- At the posology decided by the psychiatrist
- Blinded regarding the results of the phenotypic study.

The recommended starting dose for V is 75 mg given once daily. After initiating treatment, it is imperative to re-evaluate response every 2 weeks or more. In the absence of remission, it is common practice to raise the dose until one of the following situations occurs:

1. Remission of symptoms
2. Appearance of dose-limiting adverse events
3. Upper limit of the maximum recommended dose range is reached.

Patients not responding to the initial 75 mg/day dose may benefit from dose increases up to a maximum dose of 375 mg/day (300mg in outpatients).

1.6.2 The assessment of DME activity: the use of probes substrates

The drugs used in the cocktail substrates are marketed drugs for many years and their safety profile is well known.

In this study, we will use the lowest doses of these marketed drugs and the drugs will be administered only one time.

We won't change the dosage and the galenic form of drugs, neither make a single capsule integrating all these products.

Despite these low doses, the assay methods are sufficiently robust to estimate the drug and metabolites concentrations. Bosilkovska *et al.* have shown that their technique-blotting assay after administration of micro-doses of medication was effective[87].

Moreover the absence of drug interaction between these substrates has already been demonstrated [88,89].

Each of four drugs will be administered successively.

- A capsule of omeprazole 10mg
- 6.8ml of an oral liquid formulation of Dextrométhorphane bromhydrate (Tussidane 1.5mg/ml , syrup)
- 1 mg of an injectable solution of Midazolam for oral administration (Midazolam

1mg/mL, injectable solution)

- A tablet of fexofenadine 120mg

The pill and liquid formulations will be taken orally successively with a glass of water.

1.7 Summary of the known and foreseable benefits and risks for the research participants

1.7.1 The risks

V is the treatment usually followed by the patient included in the study. No other risk than those associated with the treatment of depression (and detailed in the chapter 7) is expected, and no risk is specifically associated with the study.

This research has some risk associated with the assessment of DME activity, as presented in **Table 5**. The additional risk for research participants is the appearance of a hematoma at capillary and venous ponction site. No other risks are expected.

Table 5: Summary of the known and foreseeable risks for the research

Risks associated with drug intake	
Omeprazole 10mg	At a daily dose of 20-40mg: is able to cause headache, abdominal pain, nausea, vomiting, diarrhoea or constipation.
Dextromethorphan 10mg	At a daily dose of 25mg three to four times per day, nausea, drowsiness or skin rash have been reported
Midazolam 1mg	At a daily dose of 7.5 to 15 mg it is able to induce: drowsiness, fatigue, confusion, headache, muscle weakness and rarely allergic reactions
Fexofenadine 120 mg	At a daily dose of 120-180mg, it is able to induce headache, drowsiness, dizziness and nausea.
Additional risks	
Blood sampling (2 samples of 5 mL=10mL, 1 sample of 7mL and 1 sample of 2.5mL)	Hematoma, Local Pain, Bleeding
Capillary dried blood spots (1 drop for each three samples)	Hematoma, Local Pain, Bleeding

1.7.2 The absence of direct benefits

The value of the Css of V and ODV won't be brought to the consideration of the clinician or the patient during the study for the following reasons:

- The assessment of Css of the overall population is not planned for the moment and may be performed some months after the visit.
- The therapeutic drug monitoring is not recommended in this indication in France, as no recommendation exists for their interpretation and the dosage adjustment.

The assessment of DME activity will be brought to the consideration of the clinician and/or the patient on his demand, but only at the end of the study.

1.7.3 The benefit for the population of patients with TRD

The development of a personalized medicine in psychiatry may reduce treatment failure, intolerance or resistance, and hence burden and costs of affective disorders. There is a hope that biomarkers will be found to guide treatment selection. Our study presents several benefits for the population with MDE:

- It will improve the knowledge of the factors of variability in V PK and PD and their determinants
- A simple phenotypic approach of drug metabolizing activity will be tested in the clinical settings and may be used in the future in the therapeutic management of depression.

2 OBJECTIVES

2.1 Primary objective

To study the correlation between the concentration (V+ODV) and drug metabolism variability assessed by a phenotypic approach.

2.2 Secondary objectives

To compare between responders and non-responders, as well as between patients with or without side effects:

- The CYP2C19 activity and the prevalence of each profile of metabolism
- The CYP2D6 activity and the prevalence of each profile of metabolism
- The CYP3A4 activity and the prevalence of of each profile of metabolism
- The P-gp activity and the prevalance of each profile of transport

To study the correlation between V+ODV concentration/dose and V+ODV concentration and antidepressant efficacy and tolerance

To study the correlation between the ratio ODV/V and CYP2D6 activity

To study the correlation between the concentration at 2 hours and the AUC (2,3,6 hours) of the metabolic ratio hydroxyomeprazole/omeprazole

To conduct exploratory association analyses between blood biomarkers (candidate mRNA and miRNA) and the tolerance and efficacy of V

To analyse the role of genetic variations of DNA in the determination of CYP2C19 and 2D6 phenotypes, in patients with PM profile.

3 PLAN FOR THE RESEARCH

3.1 Concise description of the primary and secondary assessment criteria

3.1.1 Primary assessment criteria

The CYP2C19 activity: 5-hydroxyomeprazole/omeprazole at 2 hours and $AUC_{2,3,6}$ of the Metabolic ratio 2, 3 and 6 hours after omeprazole oral administration

The CYP2D6 activity: dextrorphan/dextromethorphan ratio two hours after dextromethorphan oral administration

The CYP3A4 activity: 1-hydroxymidazolam/ midazolam ratio two hours after midazolam oral administration

The P-gp activity: Fexofenadine $AUC_{2,3,6}$ based on fexofenadine concentrations at 2, 3 and 6 hours after fexofenadine oral administration

Antidepressant concentrations: V+ODV

They will be assessed during Visit V1, 7-21 days after Visit V0**.**

3.1.2 Secondary assessment criteria

- Screen for tobacco use and Fagerstrom test
- Characteristics of the mood disorder
- Anxiety scale Tyrer
- QIDS-SR16
- Criteria for rating medication trials for antidepressant failure and level of resistance
- MARS score
- PRISE-M score
- FISBER score

They will be assessed during Visit V0, 0-20 days after having increased the dose of venlafaxine.

- Montgomery and Asberg Depression Rating Scale (MADRS): Patients responders to V are defined by a 50% decrease in MADRS score at 8 weeks of V treatment in comparison with MADRS score measured during patient selection.
- Hamilton Rating Scale for Depression (HAMD)

They will be assessed during the selection Visit and Visits 2 and 3

- MARS score
- PRISE-M score: Patients with side effects are defined by a PRISE-M score >10.
- FISBER score
- Current treatment

They will be assessed during the Visits 2 and 3.

3.2 Description of research methodology

3.2.1 Experimental plan

Our study is an interventional study (RBM)
Patients referred for depression in the department of psychiatry, with an on-going treatment of V will be invited to participate to the study.

3.2.2 Number of centers participating

This a multicenter study, involving 12 clinical centers (2 from AP-HP, and 9 outside), 7centers of clinical investigations, 4 centers involved in biological analysis (CHRU Besançon, France; HUG Genève, Suisse; INSERM UMR1098; INSERM UMR-S1144).

3.2.3 Responsabilities of the centers

The objectives and responsabilities of each center (clinical or centers of clinical investigations) for a same town will depend on the local organization decided by the investigators involved in the research.

Patient’s selection and inclusion will be conducted by a hospital practionner.
Visit V1 will be performed by a nurse and supervised by a hospital practitioner.
Visits V2 and V3 will be conducted by a psychologist or a hospital practitionner.

Table 6: List of participating clinical centers and their centers of clinical investigation

N° centre	Centre	Investigateur principal	Adresse
1	CHU BESANCON	Pr. Emmanuel Haffen	CHU de Besançon Service de Psychiatrie de l'Adulte 25030 BESANCON Cedex
2	AP-HP Groupe Hospitalier Universitaire Saint-Louis-Lariboisière-Fernand Widal	Pr. Frank Bellivier	Département de Psychiatrie et de Médecine Addictologique Groupe Hospitalier Universitaire Saint-Louis-Lariboisière-Fernand Widal 200, rue du Faubourg Saint Denis 75475 PARIS Cedex 10
4	CH Charles Perrens BORDEAUX	Dr. Alexandra BOUVARD	Pôle de Psychiatrie 3-4-7 du Dr. Arnaud Deloge CERPAD Centre Hospitalier Charles Perrens 121, rue de la Béchade CS 81285 33076 Bordeaux Cedex
6	CHU MONTPELLIER	Pr. Philippe Courtet	Centre Hospitalier Universitaire de Montpellier Département d'Urgences et Post Urgences Psychiatriques – Hôpital Lapeyronie 371, av. du Doyen Gaston Giraud 34295 Montpellier cedex 5
7	CIC MONTPELLIER	Dr. Florence Galtier	Hôpital Saint Eloi, CIC P-1001 80, Avenue Augustin Fliche 34295 Montpellier cedex 5
8	Hôpital de La Conception	Dr. Raphaëlle Marie Richieri	Hôpital de La Conception Pole psychiatrie adulte, addictologie, pédo-psychiatrie Service du Pr. C. Lançon- 147, Boulevard Baille 13005 Marseille
9	CIC MARSEILLE	Dr. Sophie Morange	CIC Marseille Hôpital de la Conception 147, Boulevard Baille Bâtiment Néphrologie - 3ème étage 13005 Marseille
10	CHU CLERMONT-FERRAND	Pr. Pierre-Michel Llorca	CHU Clermont-Ferrand BP 69 Hôpital Gabriel-Montpied Pôle de psychiatrie-Service du Pr Llorca 58, Rue Montalembert 63003 Clermont-Ferrand cedex
11	CHU TOURS	Pr. Wissam El-Hage	Clinique Psychiatrique Universitaire, CHRU de Tours Rue du Coq 37540 Saint-Cyr-sur-Loire

12	CIC TOURS	Pr. Wissam El-Hage	Centre d'investigation clinique CHRU de Tours Hôpital Bretonneau Batiment B2A 2, boulevard Tonnellé 37044 Tours cedex 9
13	CH Le Vinatier BRON	Dr. Rémi MOIRAND	Centre Hospitalier Le Vinatier Unité Ugo Cerletti, pôle Est, Centre Hospitalier Le Vinatier – Bât 416 – BP 300 39 - 95 Bd Pinel 69678 BRON Cedex
14	CHU GRENOBLE	Dr. Jérôme Holztmann	Pôle Psychiatrie, Neurologie et Rééducation Neurologique Clinique de Psychiatrie Hôpital Nord CHU Grenoble CS 10217 38043 Grenoble cedex 09
15	CIC GRENOBLE	Pr. Jean-Luc Cracowski	Centre d'Investigation Clinique – Inserm CIC3 Hôpital Albert Michallon CHU de Grenoble BP 217 38043 Grenoble Cedex 09
16	AP-HP CRETEIL	Dr Yon Liova	Service Intersectoriel de Psychiatrie (Dr L. YON) C.H.U H. MONDOR 51 avenue du Maréchal De Lattre de Tassigny 94000 Créteil
17	CIC CRETEIL	Dr. Philippe Le Corvoisier	Centre d'investigation clinique 51 av Mal de Lattre de Tassigny 94010 Creteil
18	CHU TOULOUSE	Dr. Antoine YRONDI	Service Universitaire de Psychiatrie et de Psychologie Médicale Hôpital de Casselardit – CHU de Toulouse TSA 40031 – 31059 Toulouse Cedex 9
19	CIC TOULOUSE	Dr. Fabienne Calvas	Centre Investigation Clinique CHU Purpan- Hôpital Pierre Paul Riquet Hall D-niveau 2 Place du Dr Baylac TSA 40031 31059 Toulouse Cedex 9
20	CHRU BREST	Dr Florian STEPHAN	Psychiatrie de liaison-Service hospitalo-universitaire de psychiatrie Hôpital Cavale Blanche Boulevard Tanguy Prigent 29609 BREST Cedex
21	CIC BREST	Dr Florian STEPHAN	Centre d'Investigation Clinique INSERM CIC1412 CHU de la Cavale Blanche 29609 BREST Cedex

The different steps of the research are summarized below:

- Reception of the fax of inclusion of the patients.
- Reception of the individual prescription of drugs that the patient will receive at V1.
- Verification of the national register of subjects participating in biomedical research.
- To schedule the V1 (outpatient or inpatient) 7-21 days after the after inclusion, the visits V2 and V3
- To receive the batches of drugs for phenotyping from the local pharmacy, and the three blotting papers and the PAQGEN for RNA analysis per patient from the URC Saint Louis,
- To supervise the nurse who will give the cocktail of drugs and collect the samples (visit V1).
- To verify the traceability of drugs administered.
- To collect blood for DNA collection, circulating RNA according the precise modalities (secondary to blood sample for V, in PAXGEN tubes, which will be checked 8-10 times, then stored 2-72 heures in vertical position at ambient temperature-18-25), and further stored in a vertical position at -20°)
- To perform the centrifugation and/or to freeze the samples of Venlafaxine and to organize their collection.
- Responsibility for the conservation of samples in a freezer at -20 °
- Organization of the sending of the samples to the dates and in the predetermined rules by the principal investigator (sending costs are provided by another budget)
- Consumables Management (Tubes only: 1 EDTA tube 7mL + 2 tubes of 5mL + 2 glass tubes for serum after centrifugation + PAXGEN tubes) necessary for study

3.2.3.1 Centers involved in biological analysis (Table 7)

Table 7: List of participating biological centres

Measurement of V and ODV	**Dosage of drugs and metabolic ratio on blotting paper**
Department of clinical pharmacology and toxicology, Pr Siamak DAVANI	Department of clinical pharmacology and toxicology, Pr DESMEULES
Centre Hospitalier Régional Universitaire Hôpital Jean Minjoz (Besançon) 2 boulevard Fleming 25030 Besançon (France) Courriel : pharmacologie@chu-besancon.fr Responsible for the analysis Dr Damien Montange Courriel: dmontange@chu-besancon.fr	Hôpitaux Universitaires de Genève Rue Gabrielle Perret-Gentil 4 1205 Genève (Switzerland) Responsible for the analysis: Youssef Daali Courriel: Youssef.Daali@hcuge.ch
RNA and DNA collection	
INSERM, EFS, Université de Franche-Comté UMR1098 Etablissement Français du Sang Bourgogne Franche-Comté 8, rue du Docteur Jean-François-Xavier Girod	

BP1937 25020 Besançon Cedex FRANCE Prof. Philippe SAAS e-mail: philippe.saas@efs.sante.fr
RNA extraction and DNA analysis
Inserm UMR-S 1144 Variabilité de Réponse aux Psychotropes Universités Paris Descartes – Paris Diderot Responsible for the analysis Pr Frank Bellivier Email: frank.bellivier@inserm.fr

3.2.4 Identification of the subjects

Each patient is identified in the study by a Subject Number (Subject N°) that is assigned when the patient has signed the Study Informed Consent Form and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The allocation of the Subject N° will be handled by the statistical data center SBIM (Service de biostatistique et informatique médicale). The Subject N° consists of the Center Number (3 numérical positions), the patient inclusion number (4 numérical positions), and patient's initials (surname / first name: 2 numérical positions).

4 PROCEDURE FOR THE RESEARCH

The procedure for the research is represented in **Figure 5** and **Figure 6**.

The other visits will be carried out as part of a traditional hospitalization if it is needed regarding the patient's psychiatric condition. Conversely, they will be done during a day hospitalization (V0 and V1) or during a consultation (V2, V3). They will be systematically supervised by a practitioner.

4.1 Selection visit

The selection visit takes place during the usual medical follow-up of patients with MDD, during a consultation or a hospitalization.

Patients with MDE non-responders to V (MADRS≥20) after 4 weeks of V regardless of the dose will be selected. Two scales of depression will be performed during this visit: MADRS and HAM-D. In accordance with the usual practice and considering its psychiatric evaluation, the referent psychiatrist (and investigator) will first propose to increase the dosage.

If the patient agrees to continue V at an increased dosage, orally taken in the morning, the investigator will give oral and written information about the study.

An inclusion visit (Visit 0) will be planned.

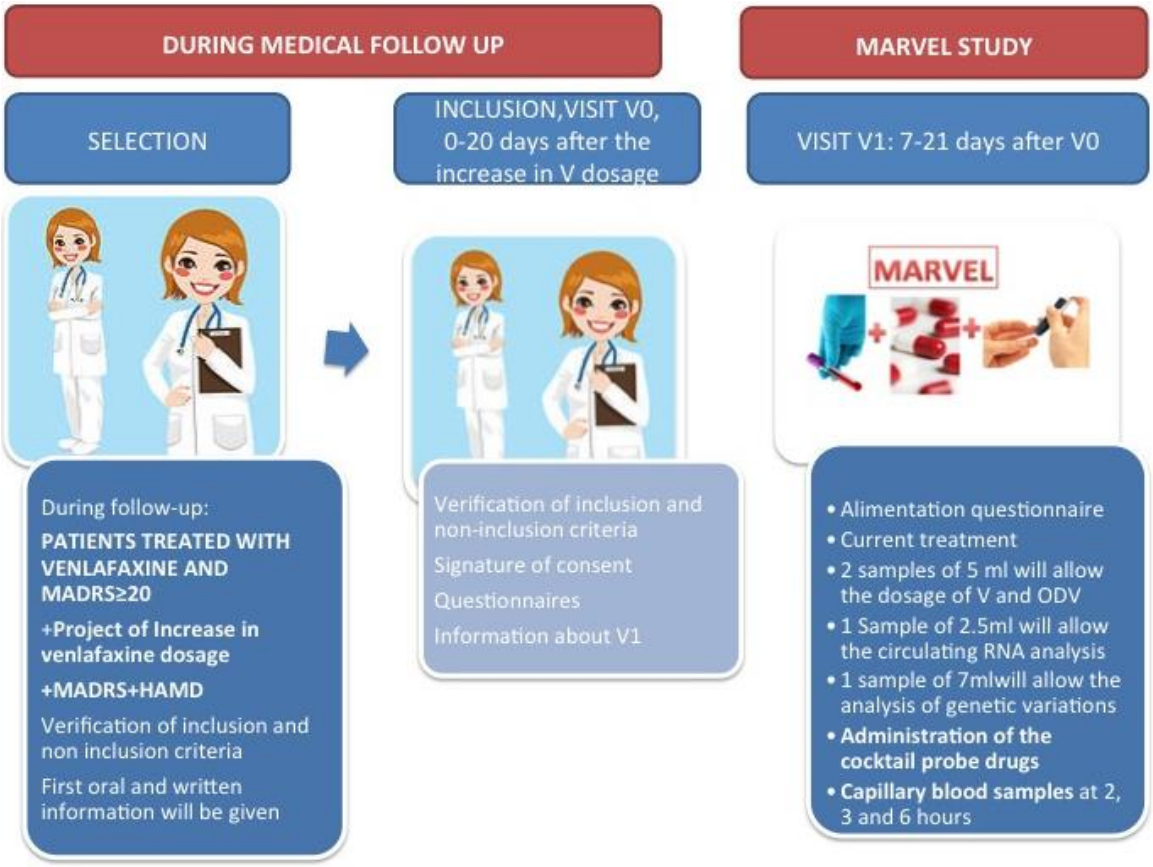

Figure 5: MARVEL study: From selection to Visit V1

4.2 Inclusion visit

The inclusion visit (V0) takes place **0-20 days** after the increase in V dosage (selection visit). During this visit with an investigator patients will be included.

The patient is evaluated against study inclusion and non-inclusion criteria. Once a patient is considered eligible to be included in the study and consent is signed the Investigator will complete the “Patient Inclusion Form” and send it to SBIM (Service de biostatistique et informatique médicale, Saint Louis). The individual prescription of drugs that the patient will receive at V1 will be signed and send to the center where the visit V1 will be performed and the patient will keep the original form of the prescription. The allocation of identification number will be handled by the statistical data center (this identification number will be retained for the entire research).

<u>The items listed below will be asesed:</u>

1. Screen for tobacco use and Fagerstrom test
2. Characteristics of the mood disorder
3. Anxiety scale Tyrer
4. QIDS-SR16
5. Criteria for rating medication trials for antidepressant failure and level of resistance
6. MARS score
7. PRISE-M score
8. FISBER score

9. List of current treatments

10. Details about the study will be given and the following recommendations to participate to the visit V1 will be explained:
    - To be perfectly observant during the delay between inclusion (visit V0) and phenotypic study (Visit V1).
    - To come with the medication diary
    - To come with the original prescription of the cocktail of drugs for the test.
    - To come for the phenotypic study after an overnight fast
    - Without having taken the usual drugs in the morning

In most case, the phenotypic study will be planned with the Center of clinical investigation (CIC). The minimal delay between Visit V0 and Visit V1 will include the time to reach steady state of antidepressant drug since the increase in V dosage. Hence, the visit V1 will take place between 7-21 days after Visit V0. This might correspond to a period of stable treatment.
The follow-up visits V2 and V3 will be planned with a psychologist or a practitioner. Visits V2 and V3 will be held in the clinical center or the center of clinical investigation according on the local organization of each center.

4.3 Follow-up Visits

The visit V1 will take place between 7-21 days after Visit V0, in the morning.
Criteria to perform the phenotypic study will be checked:

- Correct drug observance will be verified by the medication diary: an oversight a tablet of venlafaxine will not be allowed during the four days before V1
- Minimum delay of 7 days between Visit V0 and Visit V1.
- No change in V dosage or co-medications (antipsychotics only) between inclusion and Visit V1.
- Negative urinary pregnancy test. The test will be performed for women of childbearing age in the morning before cocktail administration.
- No intake of usual drugs in the morning of the cocktail administration. Fasting state since almost 12 hours. Last venlafaxine intake 20-30 hours before.

If the patient does not meet these criteria, he will be excluded from the study.

The nurse will collect 4 venous blood samples before cocktail drug administration.
- Two samples of 5ml will allow the dosage of V and ODV (heparinised capillary tubes, green)
- One sample of 7mL will allow DNA collection (EDTA tube, mauve)
- One sample of 2.5mL in PAXGEN according to standardized procedure

In the morning after an overnight fast, the nurse will give to the patients the cocktail probe drugs:
- A capsule of omeprazole 10mg
- 6.8 ml of an oral liquid formulation of Dextrométhorphane bromhydrate (Tussidane

1.5mg/ml , syrup)

- 1 mg of an injectable solution of Midazolam for oral administration (Midazolam 1mg/mL, injectable solution)
- A tablet of fexofenadine 120mg

The pill and liquid formulations will be taken orally successively with a glass of water.

Hence, the blood samples will be collected as follow:

- **Capillary blood samples** at 2, 3 and 6 hours after the cocktail administration (1 drops each hour) from a small finger prick will be collected on the DBS device described in paragraph 5.4, for the measurement of cocktail drug concentrations (drug parent and metabolites)
- Alimentation during the last week will be recorded by standardized brief questionnaire

Patients will be questioned and monitored at each blood sampling: Diziness (yes/no) ; Headache(yes/no) ; Nausea, vomiting (yes/no) , cardiac frequency (yes/no) , systolic and diastolic tension.

Breakfast will be possible 1 hour after taking the cocktail drugs.

The visits V2 and V3 will take place between 25-40 days (4 weeks) and 50-70 days (8 weeks) after Visit V0, with a psychologist or a practitioner.

They will include the measure of treatment adherence, tolerance and efficacy.

- MADRS
- HAMD
- FIBSER AND PRISE-M score
- MARS score, pill count
- List of current treatments and treatments received between visits (psychotropic and non-psychotropic drugs). Dates of changes.
- QIDS-SR16

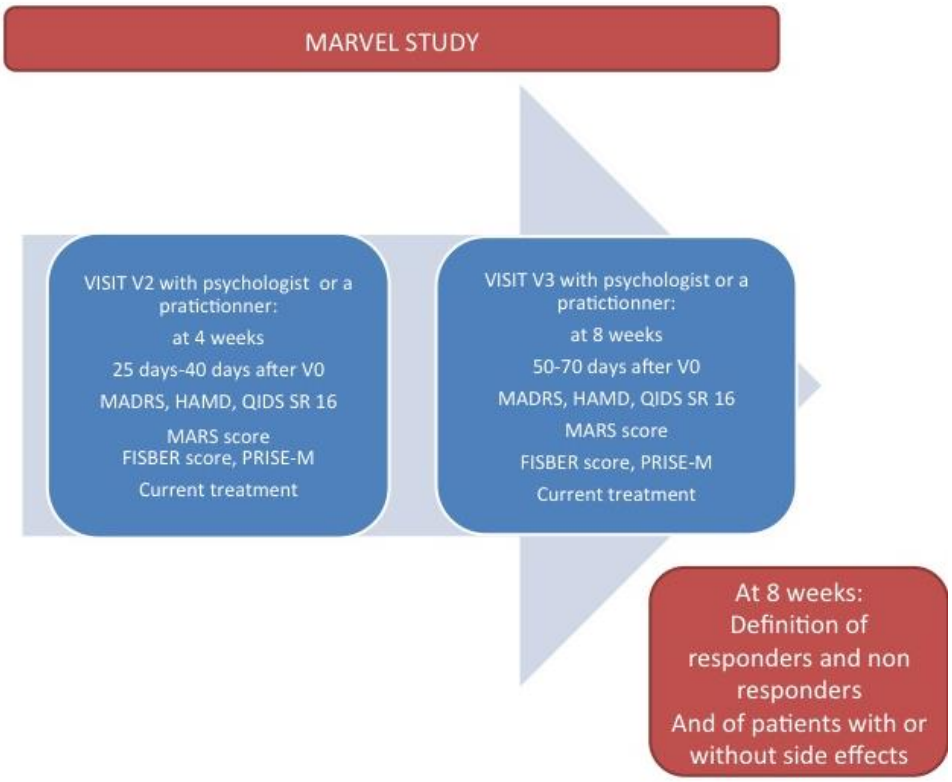

Figure 6: MARVEL study: Visit V2 and V3

4.4 Evaluation criteria

4.4.1 Phenotype

4.4.1.1 Acquisition of capillary blood collection

Nurses will perform the phenotypic study.

To simplify the process of capillary blood collection, a device has been developed by the DBS System Sàrl company (Switzerland). The prototype integrates a patented microfluidic plate (WO/2013/144743) allowing for the accurate volume control and a conventional filter paper card for blood storage (**Figure 7**). Using this novel device, 10 µL-DBS samples can be easily generated from capillary blood drop without additional manipulation. Preliminary results show excellent performances in terms of precision of collected volume and ease of use.

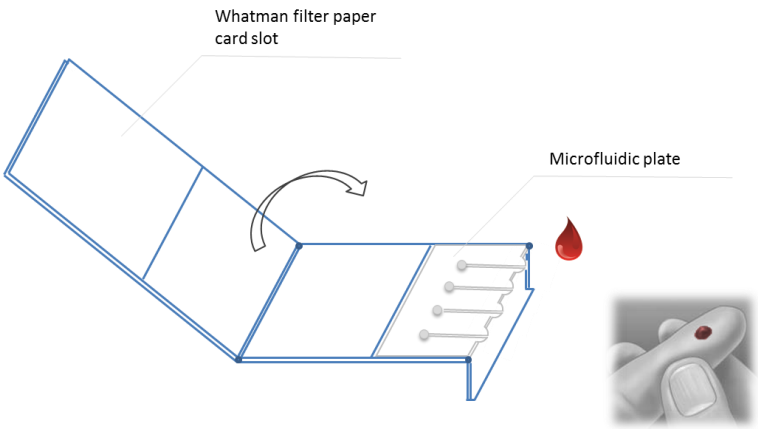

Figure 7: illustration of the new device developed by DBS System allowing for the accurate DBS collection (patent pending)

4.4.1.2 Methods of quantification

The cocktail substrates and their CYP-specific metabolites will be quantified in DBS using a single reverse- phase high-performance liquid chromatography–tandem mass spectrometry method operating in dual electrospray ionization mode, as previously described[89]. The substances of interest will be extracted from DBS samples using methanol, whereas protein precipitation using acetonitrile will be used for plasma extraction. The method has been fully validated according to international criteria.

4.4.1.3 Determination of enzymatic activities

DBS devices will be frozen at -20°C until transport and analysis. The enzymatic activities will be assessed by specific metabolite/probe concentration ratios (metabolic ratios-MR) from the sample taken 2h after cocktail administration.

CYP2C19: 5-hydroxyomeprazole/omeprazole

CYP2D6: dextrorphan/dextromethorphan

CYP3A4: 1-hydroxymidazolam/midazolam

P-gp and CYP2C19 activity will be assessed by the determination of a limited sampling fexofenadine and OHomeprazole/omeprazole AUC from the sample taken 2-3 and 6h after cocktail administration.

The cocktail substrates and their CYP-specific metabolites will be quantified in DBS using a single reverse- phase high-performance liquid chromatography–tandem mass spectrometry method operating in dual electrospray ionization mode, as previously described [87,89]. The substances of interest will be extracted from DBS samples using methanol, whereas protein precipitation using acetonitrile will be used for plasma extraction. The method has been fully validated according to international criteria.

The phenotype will be determined according to the results of the MR, and based on the results of previous studies [87] (**Table 8**).

For example, a patient with a CYP2C19 UM metabolizer profile is defined by a metabolic ratio over 4.5 based on the results of previous studies[87] .

The blood samples for drug analysis will be sent to the HUG, Suisse, each thwo months during the study, from each center.

Table 8: Definition of phenotypes according to the values of MR

2C19	**PM**		**EM**	**UM**
2h	<0.4		0.4-4.5	>4.5
2D6	PM	IM	EM	1.1 IM
2h	<0.07	0.07-2	2-10	>10
3A4	inhibited		normal	inducted
2h	<0.3		0.3-2.5	>2.5
P-gp	inhibited		normal	inducted
AUC2,3,6,	>220		65-220	<65

4.4.2 Drug concentration

Blood samples will be centrifuged and serum will be collected in glass tubes. They will be frozen at -20°C until transport and analysis. Plasma concentration will be quantified using

"Liquid chromatography coupled to tandem mass spectrometry" at the Laboratory of Toxicology, Besancon.

The blood samples for Venlafaxine and ODV Css will be sent to the laboratory of toxicology every six months during the study, from each center.

4.4.3 DNA collection and circulating mRNA

DNA: Blood samples will be conserved in a 7mL EDTA tube.
RNA: Blood samples will be conserved in PAXGEN tubes at ambient temperature 2-72h in vertical position. Then, they will be frozen at -20°C until transport (every 6 months) to the unit of INSERM, EFS, Université de Franche-Comté UMR1098. At the end of the study, the blood sample will be sent for extraction and analysis at the INSERM U1144, Universités Paris Descartes – Paris Diderot.

4.4.4 Assessment of depressive symptoms, antidepressant efficacy and adherence

4.4.4.1 Brief scale for anxiety (Tyrer),

The brief scale for anxiety of Tyrer is a subdivision of the comprehensive psychopathological scale [90]. It is a clinical interview rating scale designed to assess the psychology and somatic symptoms of anxiety; the interviewer rates the subject on each of 10 symptoms on a 7-point scale from 0 (no occurrence of the symptom) to 7 (incapacitation by lack of control of the symptom).

4.4.4.2 The characteristics of mood disorders, the screen for tobacco use and Fagerstrom test

They are standarized questionnaires included in the first evaluation of patients.

4.4.4.3 Criteria for rating medication trials for antidepressant failure

The ATHF consists of scoring instructions and ratings for most antidepressants augmentation and Electro convulsivo therapy trials. It is being used increasingly to determine the adequacy of antidepressant trials.

4.4.4.4 MADRS (Montgomery and Asberg Depression Rating Scale)

The MADRS is a ten-item diagnostic questionnaire which psychiatrists use to measure the severity of depressive episodes in patients with mood disorders[77]. It was designed in 1979 by British and Swedish researchers as an adjunct to the Hamilton Rating Scale for Depression (HAMD), which would be more sensitive to the changes brought on by antidepressants and other forms of treatment than the Hamilton Scale was. There is, however, a high degree of statistical correlation between scores on the two measures.
Each item is coted 0 to 6 by the physician. The maximal score is 60.
Depression is defined by a score ≥ 15.
MADRS remission is defined by a score less than 10[78].

4.4.4.5 Hamilton Rating Scale for Depression (HAMD)

The HAMD is a multiple item questionnaire used to provide an indication of depression, and as a guide to evaluate recovery [91,92]. The questionnaire is designed for adults and is used to rate the severity of their depression by probing mood, feelings of guilt, suicide ideation,

insomnia, agitation or retardation, anxiety, weight loss, and somatic symptoms.
Initially considered the "Gold Standard" for rating depression in clinical research, his scale should not be used as a diagnostic instrument.
The original 1960 version contains 17 items to be rated (HRSD-17), but three other questions are not added to the total score and are used to provide additional clinical information. Although Hamilton's original scale had 17 items, other versions were developed to include up to 29 items (HRSD-29). Each item on the questionnaire is scored on a 3 or 5 point scale, depending on the item, and the total score is compared to the corresponding descriptor.
Remitters from MDD were defined as HAM-D scores less than 10[93] (**Table 9**).

Table 9: Definition of remitters and responders

	MADRS	HAMD
Responders	50% decrease in score after 8 or 12 weeks of treatment	
Remitters	MADRS<9	HAMD<10

4.4.4.6 Adverse reaction Self report, FIBSER AND PRISE, auto-questionnaire

It has been reported that adverse reactions to antidepressants can be reliably assessed by self-report[94]. Most complaints listed as adverse reactions in people with depression are more common when they were medication-free rather than during their treatment with antidepressants[94]. The Frequency, Intensity, and Burden of Side Effects Rating (FIBSER) Scale, was developed to document these three domains of side effects in patients treated in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) project. The FIBSER is a reliable and valid self-report measure of side effects in a population receiving treatment for depression. Although it does not measure the impact of specific side effects, it does measure three domains of impact: frequency, intensity, and burden of the side effects. Its brevity makes it a useful tool for routine clinical practice[95].
Side effects are evaluated with Patient Rated Inventory of Side Effects (PRISE-M)[96]. PRISE is a 31-item checklist of side effects rated for the last 7 days, classified by symptoms domain i.e. gastrointestinal, heart, skin, nervous system, eyes/ears, genital/urinary, sleep, sexual functioning, and other. Each domain has multiple symptoms that can be endorsed. For each domain the patient rates whether or not the symptoms are absent (0) tolerable (1) or distressing (2). A total score defines a global side effects level, which takes into account the frequency and severity of each side effect. The frequency (% patients with the side effect tolerable or distressing) and severity of each side effect or of each domain can also be calculated.

4.4.4.7 The Medication Adherence Report Scale (MARS)

The MARS scale is a ten-item self-report measure of medication adherence, initially developed for schizophrenia [97].

4.5 End of research visit

The study will end after the assessment of response to V, after visit V3.

4.6 Expected length of participation and description of the chronology and duration of the research

Beginning of inclusion: July 2016
End expected of inclusion: January 2023

4.7 Chronology of the research

This is depicted in **Table 10**.

Table 10: Chronology and duration of the research

Maximal period between selection and inclusion	20 days
The included subjects' length of participation	70 days maximum
Inclusion period	78 months
Total research period	78 months+70 days=2442 days

4.8 Distinction between care and research

Our study is an interventional study, because the administration of drugs and genotypic analysis, as well as the determination of drug concentration, is not performed in the care of patients.

Additional questionnaires to the usual care will also be included in the study to assess the adherence to treatment, the efficacy and the tolerance (**Table 11**).

TABLE 11: Table summarising the chronology of the research and **distinction between procedures associated with "care" and procedures added because of the "research "**

Criteria	Selection: Psychiatry consultation or hospitalization	Visit V0: Psychiatry 0-20 days after decision of drug dosage increase	Visit V1: With a nurse Period: 7-21 days after V0	Visit V2: With a Psychologist or a practitioner: 25-40 days (4 weeks) after V0	Visit V3: With a Psychologist or a practitioner: 50-70 days (8 weeks) after V0
Oral and written Information about the protocol	MARVEL	MARVEL			
Verification of inclusion and non inclusion criteria	MARVEL	MARVEL			
Signature of informed consent		MARVEL			
MADRS and HAM-D	Care			MARVEL	MARVEL
Screen for tobacco use and Fagerstrom test		MARVEL			
Characteristics of the mood disorder		MARVEL			
Anxiety scale Tyrer		MARVEL			
Criteria for rating medication trials for antidepressant failure		MARVEL			
QIDS-SR16		MARVEL		MARVEL	MARVEL
MARS score		MARVEL		MARVEL	MARVEL
PRISE-M score		MARVEL		MARVEL	MARVEL
FIBSER score		MARVEL		MARVEL	MARVEL
Urinary pregnancy test			MARVEL		
Current treatment		MARVEL	MARVEL	MARVEL	MARVEL
Recent alimentation			MARVEL		
Blood sample for Css of V and ODV, DNA and mRNA			MARVEL		
Cocktail of drugs* administration			MARVEL		
Blood sample for Phenotypic study			MARVEL		
Total amount of blood for the research			19.5 mL of venous blood and 3 drops of capillary blood sample		

*fexofenadine, midazolam, dextromethorphan, omeprazole

4.9 Biological Collection

The samples (serum bank, DBS collection system) taken as part of the research will be included in a biological collection, until their analysis (Table 12).
In most case the collection(s) will be stored at the center of clinical investigation (CIC) linked to the recruiting center under the supervision of their responsible (name and address of each location where the collection will be stored is given in Table 7) until sending the samples (tubes or blotting papers) for their analysis in the respective laboratories.
The samples may be used with the explicit agreement of the subject on the consent form.
The collection will be declared to the ANSM in the context of biomedical research.

Table 12: Nature of the biological collection and its outcome

Type of sample	Quantity	Storage location	Purpose of the collection	Storage period
Blood sample for Css of V and ODV	2x5mL Centrifugation conservation in glass tubes	Each CIC Freezer -20°C (in vertical position for PAXGEN)	. Measuring of drug concentration	10 years
Blood sample for circulating mRNA (PAXGEN)	1x2.5mL Ambient temperature 2-72h in vertical position		Studying the gene expression of proteins involved in drug disposition	20 years
Blood sample for DNA analysis	1x7mL		Studying the allelic variation of genes encoding for proteins involved in drug disposition	
Blood sample for Phenotypic study	Dried blood spots device			Until analysis and destroyed immediately after

4.10 Termination rules

After the Visit V3, the patient will continue his usual follow-up with the unit of psychiatry and/or the usual psychiatrist. The change or the maintenance of V will be decided according to the psychiatric follow-up only, and not on the results of the study.
The study does not modify the care of the patient.
However:

- Any subject can withdraw from participating in the research at any time and for any reason.
- The investigator can temporarily or permanently end a subject's participation in the research for any reason that affects the subject's safety or which would be in the subject's best interests.

If an included subject leaves the research prematurely before Visit 1 or does not meet the criteria to perform V1, he will be excluded and replaced by another patient.
If an included subject leaves the research prematurely before Visit 3, he will be considered as lost of follow-up, and the data will be analysed in intention-to treat.
Data related to the subject can be used unless an objection was recorded when the subject signed the consent form.
If the treatment by V is stopped after V1 and before Visit V3 for reasons independent from the study (side effects, drug interaction, inefficacy etc), the patient will stay in the study and the data will be analysed in intention-to treat.

The case report form must list the various reasons for ending participation in the research:

- Not the all criteria to perform Visit V1
- Medical problem requiring hospitalization other than in psychiatry department
- Subject's personal reasons
- Other investigator's reasons
- Explicit withdrawal of consent
- Lost of follow-up

4.10.1 Follow-up of the subjects after the premature termination of treatment

The patient will continue his follow-up by the unit of psychiatry and/or the usual psychiatrist. The change or the maintenance of V will be decided according to the psychiatric follow-up only, and not on the results of the study.

4.10.2 Methods for replacing subjects, if applicable

All patients included who does not meet the criteria for phenotypic study (Visit V1) will be replaced by another patient.
If V is stopped before Visit V3, the date of the last intake will be notified and the patient will participate to the rest of the study, until Visit V3.

4.10.3 Terminating part or all of the research

Not applicable

5 ELIGIBILITY CRITERIA

5.1 Inclusion criteria

- Patient (Hospitalized or outpatient) with major depressive disorder and MADRS ≥ 20 at visit of selection
- Patients non responders to V after 4 weeks of V regardless of the dose
- Decision of the psychiatrist to increase the dose of V at visit of selection
- Male and female Age ≥ 18 years Understanding of French language and able to give a written inform consent.
- Informed consent signed to participate to the study
- Individuals covered by social security regimen

5.2 Non-inclusion criteria

- Patients treated by more than one antidepressant other than mirtazapine or

mianserine

- Patients currently treated with one of the drug substrate of the cocktail and/or by esomeprazole
- Sensitivity or contra indication to any of the substrate drugs used
- Current pregnancy or desire to get pregnant, or breastfeeding
- Bipolar disorder and schizophrenia

5.3 Recruitment methods

The recruitment method has been previously detailed in paragraph 4.

Patients will be recruited in 10 departments of psychiatry during their usual follow-up (Table 13). All of them are affiliated to the FondaMental foundation network for resistant depression. This affiliation contributes to increase the number of patients addressed in the respective department of psychiatry for resistant or non-resistant depression. According to the European Medicines Agency, a patient has been considered suffering from treatment resistant depression (TRD) when consecutive treatments with two antidepressants of different pharmacological classes, used for a sufficient length of time at an adequate dose, failed to induce a clinically meaningful effect (non-response) [98].

Both patients with and without the criteria of TRD will be included in this study if they meet the inclusion criteria for the study. Some questionnaires will be common between those used in the FondaMental Network and those used in the MARVEL study.

Since their beginning 6 months ago, the centers have been able to include 80 patients in the FondaMental Network. An exponential increase in the number of patients included in the network is expected.

As 80 patients have been included in this network in its first 6 months and as this activity is only 10 to 20% of the activity of the psychiatry departments for depression, we are confident on the ability of the centers to include 205 patients receiving V during two years.

V is one of the three most prescribed drugs in France, after escitalopram and paroxetine, and is approximately 16% of the overall antidepressant prescribed in France.

Table 13: Expected number of enrolled subjects in the study

	Number of subjects
Total number of subjects expected	205
Number of centers	19
Inclusion period (months)	78 months
Number of subjects/center	19 subjects
Number of subjects/center/month	0.9 subject

5.3.1 Recruitment of patients for the study

It has been detailed in the paragraph 4 (procedure for the research). Briefly, hospitalized patients or outpatients will be recruited during their usual follow-up.

6 TREATMENT ADMINISTERED TO RESEARCH PARTICIPANTS

6.1 Description of the experimental treatment

Venlafaxine is considered as an experimental treatment in this research.

However, the supply of Venlafaxine by the sponsor “APHP” is impossible for these differents reasons:

- Initiation of Venlafaxine is before inclusion of patients in the study and the duration of treatment is more important than duration of participation of patients.
- Dose selection is at the discretion of the psychiatrist. There are different dosages of Venlafaxine.
- Visits of dosage adjustment are different of formalized study visits
- Treatment will be delivered by city pharmacies.

According to the Article L 1121-16-1 of the French Public Health Code, institutional sponsor has the option not to provide treatment used in conditions for entitlement to reimbursement by the health insurance. Treatment is prescribed in accordance with the recommandations.

So, Venlafaxine won’t be provided and labelled by the sponsor “APHP”.

We propose an approach based on alternative traceability for Venlafaxine (This is detailed in the paragraph 6.3)

6.2 Description of the non-experimental treatment

In the morning after an overnight fast, during the visit V1 and only one time during the study, patients will be given the cocktail probe drugs, by oral route

- A capsule of omeprazole 10mg
- 6.8 ml of an oral liquid formulation of Dextrométhorphane bromhydrate (Tussidane 1.5mg/ml , syrup)
- 1 mg of an injectable solution of Midazolam for oral administration (Midazolam 1mg/mL, injectable solution)
- A tablet of fexofenadine 120mg

As many drugs necessary for the cocktail are not available in the hospital pharmacy, they need to be bought specifically. There is no substitution possible between generic medicines.The sponsor will provide these marked drugs.

Treatments will be labelled and supplied to the pharmacies at each center, by the Clinical Trial Department of EP-HP, AGEPS.

6.2.1 Omeprazole 10mg, gastro-resistant capsule (A02BC01)

Omeprazole is a well-known proton pump inhibitor, which decreases gastric acid secretion by inhibiting the H+/K+-ATPase in the gastric parietal cells. Omeprazole is rapidly absorbed after oral administration with peak plasma concentrations achieved within 30 minutes. The elimination half-life is approximately 1 hour. The inactive metabolites of omeprazole are eliminated in urine and faeces [99].

Proton pump inhibitors are generally well tolerated. The most common adverse reactions

reported include headache, abdominal pain, nausea, vomiting, diarrhoea, constipation and rash.
The recommended daily dose for the treatment of gastric or duodenal ulcer is 20 to 40 mg. The administered dose during this study is 10 mg. Hence, it will be administered to a 2 to 4 time lower dose than usual dose.
Omeprazole 10mg must be kept at a temperature < 25°C.

6.2.2 Tussidane 1.5mg/ml , syrup (R05DA09)

Dextromethorphan is an opioid used as an antitussive drug. Unlike other opioids, dextromethorphan is a very weak μ-agonist and is thus not used as analgesic. It is also exempt of euphoriant effects and physical dependence at the dose administered in this study (10,2 mg).
Dextromethorphan is rapidly and almost completely absorbed after oral administration. The maximal plasmatic concentrations are achieved 2-3 hours after the administration. The elimination half-life of dextromethorphan is variable and depends on the polymorphic phenotype.
Adverse effects with standard doses of dextromethorphan are rare, but nausea and/or other gastro-intestinal disturbances, slight drowsiness, and dizziness sometimes occur.
The usual dose of dextromethorphan as an antitussive drug is 25 mg 3 to 4 times a day. A dose of 10,2 mg will be administered. Hence, it will be administered to a 7 to 10 time lower dose than usual dose.
Tussidane 1.5mg/ml must be stored at room temperature.

6.2.3 Midazolam 1 mg/mL, injectable solution (N05CD08)

Midazolam is a benzodiazepine. As the other members of this drug class, midazolam has anxiolytic, hypnotic, sedative and myorelaxant effects. After oral administration midazolam is rapidly absorbed (absorption half-life is 5 to 20 minutes). The maximal plasmatic concentration is achieved approximately 1 hour after oral administration. The elimination half-life of midazolam is between 1.5 and 2.5 hours.
The most frequent adverse effects, common to all benzodiazepines, include: drowsiness, fatigue, mental confusion, headache, muscular weakness and ataxia. Rarely, allergic reaction (rash for example) might occur. Repeated administration of midazolam can lead to a physical dependence.
The usual single dose recommended is 7.5 to 15 mg. In this study midazolam will be administered as a 1 mg single dose (10 times lower than the usual dose). Thus, adverse reactions are not expected to occur.
Midazolam 1mg/mL must be stored at room temperature, out of direct light.

6.2.4 Fexofenadine 120mg, film-coated tablet (R06AX26)

This drug is a non-sedating histamine H1-receptor antagonist used for the treatment of seasonal allergic rhinitis and chronic urticaria. The dose administered in this study is 25 mg. Fexofenadine is rapidly absorbed after oral administration with maximal plasmatic levels achieved after 1 to 3 hours. This drug does not undergo significant biotransformation and is excreted unchanged in the urine and faeces.
Fexofenadine is generally well tolerated. Reported side effects include headache, drowsiness, vertigo and nausea.
Usual daily doses are 120 to 180 mg. In this study fexofenadine will be administered as a

120 mg single dose (1-1.5 times lower than the usual dose).
Fexofenadine 120mg must be stored at room temperature.

6.3 Description of the traceability elements that accompany the medications

A patient diary is given to each patient in order to trace administration of Venlafaxine during the study. Trade name with dosage, batch number and expiry date must be reported. Data of the patient diary will be monitored by the sponsor.
The treatment units of the cocktail will be stored in the Clinical Trial Department of EP-HP, AGEPS, and sended to the pharmacies at each center. The traceability elements will be collected in the CRF of each patient.

6.4 Authorised and prohibited treatments (medicinal, non medicinal, surgical), including rescue medications

The respective contra-indication of omeprazole, dextromethorphan, midazolam and fexofenadine (**Table 15**) will be respected, all along the study. No treatment will be prohibited as the study is naturalistic. A questionnaire about the alimentation the week before cocktail administration will be given the day of the Visit V1.

6.5 Methods for monitoring compliance with the treatment

6.5.1 MARS score and additional measures to assess adherence

The Medication Adherence Rating Scale (MARS) is a ten-item self-report measure of medication adherence in psychosis, validated in French version, and also used in depression.[100,101])(Appendix).

6.5.2 Medication Diary

A medication diary will be given to the patient the day of inclusion (V0) and will be verified at V1.

Table 15: Contra indications of substrates used for phenotypic study

Treatment	Contra indications
Omeprazole	Hypersensitivity to omeprazole, substituted benzimidazoles or to any of the excipients. Omeprazole like other proton pump inhibitors (PPIs) must not be used concomitantly with nelfinavir
Dextromethorphan	Hypersensitivity to the active substance or to any of the excipients. Dextromethorphan must not be initiated for at least 14 days after discontinuation of treatment with an irreversible MAOI.
Midazolam	Hypersensitivity to the active substance or to any of the excipients. Acute narrow-angle glaucoma and open-angle glaucoma without treatment. Depression of vital signs and acute alcohol intoxication. Respiratory disease.
Fexofenadine	Hypersensitivity to the active substance or to any of the excipients.

The circuit of the biological samples is summarized in Table 16.

Table 16: Circuit of the investigations

Type of Investigations	Storage location and responsible	Destination for analysis	Destination of the written result
Blood sample for Css of V and ODV	Each CIC or clinical center (Table 7) until the send of the samples every 6 months	Pharmacology and toxicology Besancon	CRF
Blood sample for DNA and circulating mRNA	Each CIC or clinical center (Table 7) until the send of the samples every 6 months	INSERM, EFS, UMR1098 Besançon INSERM UMR-S1144 Paris	CRF
Blood sample for Phenotypic study	Each CIC or clinical center (Table 7) until the send of the samples every 2 months	Pharmacology Toxicology Geneva, Switzerland	CRF

7 SAFETY ASSESSMENT - RISKS AND RESTRICTIONS ADDED BY THE RESEARCH

7.1 Description of parameters for assessing safety

Patients will only be questioned and monitored at each blood sampling during Visit V1: **Diziness (yes/no); Headache (yes/no); Nausea, vomiting (yes/no) , cardiac frequency, systolic and diastolic tension.**

The patients will be asked to contact us in case of an adverse event occurring during the 48 hours following the visit V1.

No additional parameters related to the research, as no other events related to the research are expected. The patients will be questioned about their tolerance of Venlafaxine, but no additional riks factor for adverse event due to V is expected due to the research.

7.2 Anticipated methods and timetable for measuring, collecting and analysing the parameters for assessing safety

Patients will be questioned and monitored at each blood sampling:

at the beginning, **then 2, 3 and 6 hours** after oral administration of the drug cocktail:

Diziness (yes/no); Headache (yes/no); Nausea, vomiting (yes/no) , cardiac frequency, systolic and diastolic tension.

The patients will be asked to contact us in case of an adverse event occurring during the 48 hours following the visit V1.

No additional parameters related to the research, as no other events related to the research are expected. The patients will be questioned about their tolerance of Venlafaxine, but no additional riks factor for adverse event due to V is expected due to the research.

7.3 Procedures in place for recording and reporting adverse events

7.3.1 Definitions

<u>According to Article R1123-39 of the French Public Health Code and the guideline on good pharmacovigilance practices (EMA, 2012):</u>

Adverse event: Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

❖ **Adverse drug reaction**
Any response to a medicinal product, which is noxious and unintended.

❖ **Serious adverse event**
Any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

❖ **Unexpected adverse reaction**
An adverse reaction, the nature, severity or outcome of which is not consistent with the applicable product information: the summary of product characteristics (SmPC) for an authorised product or the investigator's brochure for an unauthorised investigational product.

<u>According to the notice to sponsors of clinical trials for medications (ANSM)</u>:

❖ **New safety issue**

Any new information regarding safety:

- that could significantly alter the assessment of the benefit-risk ratio for the medication, or for the trial
- or which could lead to the possibility of altering the administration of the medication or altering the conduct of the trial

<u>Examples</u>
a) Any clinically significant increase in the frequency of an expected serious adverse reaction occurring
b) Suspected unexpected serious adverse reactions (SUSAR) occurring in patients who have finished the trial and about whom the sponsor is notified by the investigator, who also provides any follow-up reports
c) Any new fact relating to the conduct of the clinical trial or the development of the medication, if the new fact is likely to affect participant safety
d) Recommendations from the data safety monitoring board (DSMB), if applicable, if they are relevant to the safety of the participants
e) Any unexpected serious adverse reaction reported to the sponsor by another sponsor of a trial carried out in a different country but relating to the same medication

7.3.2 The investigator's roles

7.3.2.1 Regulatory obligations of the investigator (Art R1123-54 of the French Public Health Code)

The investigator must notify the sponsor, **immediately on the day when the investigator becomes aware**, of all the serious adverse events, except those that are listed in the protocol (see. section 7.3.3.1)
These serious adverse events are recorded in the "adverse event" section of the case report form and the investigator must immediately notify the sponsor's Vigilance division.

7.3.2.2 The investigator's other roles

The investigator must document the serious adverse event as thoroughly as possible and provide the medical diagnosis, if possible.
The investigator assesses the severity of the adverse events as follows:

- *Mild: tolerated by the patient, does not interfere with daily activities*
- *Moderate: sufficiently uncomfortable to affect daily activities*
- *Serious: preventing daily activities*

The investigator assesses the causal relationship between the serious adverse events and the medication(s).

7.3.3 Specific features of the protocol

All serious and non-serious adverse events must be reported in the CRF.

7.3.3.1 Serious adverse events that do not require the investigator to immediately notify the sponsor

These serious adverse events are only recorded in the "adverse event" section of the case report form.

- **Normal and natural evolution of the pathology**

• Scheduled hospitalization for monitoring depression
• Hospitalization for routine treatment or for monitoring of the disease studied not associated with a deterioration of the subject
• Worsening of depression
• Suicide attempt (not completed)

- **Special circumstances**

• Hospitalization for pre-existing disease
• Hospitalization for medical or surgical treatment planned before the research
• Admission for social or administrative reasons
• Crossing emergency (<12 hours)

Adverse events likely to be associated with the treatments prescribed as part of the patient's care during the monitoring of the research

7.3.3.2 Serious adverse events that require the investigator to immediately notify the sponsor

The investigator must report immediately all adverse events that meet one of the seriousness criteria below, except for events listed in section 7.3.3.1 as not requiring immediate notification to the sponsor:
1- Death
2- Life threatening situation
3- Requiring hospitalisation or prolonging hospitalisation
4- Persistent or significant disability or incapacity
5- Congenital abnormality or birth defect
6- Or any other adverse event considered "medically significant"

- For serious adverse events related to the non experimental medication(s) and which are expected: the summary of the products characteristics (SmPC) for the following drugs, found in Appendix X, should be consulted.
- Omeprazole 10mg, gastro-resistant capsule
- Tussidane 1.5mg/ml , syrup
- Midazolam 1mg/mL, injectable solution
- Fexofenadine 120mg, film-coated tablet

- For serious adverse events related to the experimental medication Venlafaxine and which are expected: the SmPC of Effexor LP37,5 mg® should be consulted.

7.3.4 Procedures and deadlines for notifying the sponsor

Notification of an SAE must initially be provided in a written report using the special form for reporting SAE. The report must be signed by the investigator.
Each item in the form must be completed by the investigator so that the sponsor can carry out the appropriate analysis.
This initial notification must be followed by one or more detailed follow-up report(s), in writing and signed, within a maximum of 8 days in the case of a fatal or life-threatening event and within 15 days for all other cases.
Whenever possible, the investigator will provide the sponsor with any documents that may be useful (medical reports, laboratory test results, results of additional exams, etc.). These documents must be made anonymous. In addition, the documents must include the following: research acronym, number and initials of the subject, nature and date of the serious adverse event.
Any adverse event will be monitored until fully resolved (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the subject has left the trial.

The initial notification, the SAE follow-up reports and all other documents must be sent to the sponsor via fax only to the Vigilance Division of the DRCD, fax No. **01 44 84 17 99**.

The investigator must comply with all requests from the sponsor for additional information.

For all questions relating to the notification of an adverse event, the Vigilance Division of the DRCD can be contacted via email: vigilance.drcd@drc.aphp.fr

7.3.5 Period for notifying the sponsor

The investigator must report all SAE that occur in research subjects, from the moment the cocktail drugs is administered at Visit V1, until 48 hours later.

7.3.6 The sponsor's roles

The sponsor, represented by its Vigilance Division, continuously assesses the safety of each medication throughout the research.

7.3.6.1 Analysis and declaration of serious adverse events

The sponsor assesses:

- the seriousness of all adverse events reported
- the causal relationship of these events with each medication and/or specific medical procedures/exams added by the research and with other possible treatments
- the expected or unexpected nature of these adverse reactions

All serious adverse events, which the investigator and/or the sponsor believe could reasonably have a causal relationship with the medication, are considered as suspected adverse reactions.

All suspected unexpected serious adverse reactions (SUSAR) are declared by the sponsor, within the legal time frame, to the Agence Française de Sécurité Sanitaire des Produits de Santé (ANSM, French Health Products Safety Agency) and to the relevant Comité de Protection des Personnes (CPP, ethical committee).

- The initial declaration must be made no later than 7 calendar days after the date on which the serious adverse event occurs in the case of death or of a life-threatening diagnosis.
- The initial declaration must be made no later than 15 calendar days after the date on which the serious adverse event occurs in the case of other serious situations.
- The follow-up declaration must be made no later than 8 days after the 7- or 15-day deadline (depending on the seriousness).

Any suspected unexpected serious adverse reaction must also be declared electronically in the Eudravigilance European database for adverse events due to medications, established by the European Medicines Agency (EMA).
The sponsor must notify all relevant investigators about any data that could adversely affect the safety of the research subjects.

7.3.6.2 Analysis and declaration of other safety data

This relates to any safety data or new fact that could significantly alter the assessment of the benefit-risk ratio for the medication, or for the research, or which could lead to the possibility of altering the administration of the medication or altering the conduct of the research.

New facts must be declared to the competent authorities within 15 calendar days of the sponsor becoming aware. Additional relevant information must be sent within an additional 8 days after the 15 days deadline.

7.3.6.3 Annual safety report

Once a year for the duration of the clinical trial, the sponsor must draw up an annual safety report (Development Safety Update Report - DSUR), which includes, in particular:

- An analysis of the safety of the research subjects
- A description of the patients included in the trial (demographic characteristics, etc.)
- A line listing of suspected serious adverse reactions that occurred during the period covered by the report
- A cumulative summary tabulation of serious adverse events that have occurred since the start of the research

The report must be delivered no later than 60 days after the anniversary of the date on which the ANSM authorised the trial.

8 DATA MANAGEMENT

8.1 Data collection methods

The investigator will permit the sponsor's representatives to monitor the study at the frequency defined in the contract, depending on enrolment at each center.
Case Report Forms (CRFs) and related source documents will be reviewed in detail during monitoring visit (completeness, adherence to the guidelines, accuracy compared to source documents). The sponsor's representative will also review regulatory documents, drug storage and accountability.
The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by sponsor's monitors or representatives of other regulatory agencies.

8.2 Identification of data collected directly in the CRFs and that will be considered as source data

Visit V0

- Screen for tobacco use and Fagerstrom test
- Characteristics of the mood disorder
- Anxiety scale Tyrer
- QIDS-SR16
- Criteria for rating medication trials for antidepressant failure and level of resistance
- MARS score
- PRISE-M score
- FISBER score
- List of current treatments

Visit V1

- Date of Visit V1
- Number of hours since the last venlafaxine intake
- During test: Diziness; Headache; Nausea, vomiting, cardiac frequency, systolic and diastolic tension
- St john's wort use

- Grapefruit juce use, tisanes contenant du Millpertuis.
- Venlafaxine dose
- Other treatments: treatment 1, treatment 2 etc…
- Anxiolytics
- Lithium
- Antipsychotic
- CYP2C19 metabolic ratio and phenotype
- CYP2D6 metabolic ratio and phenotype
- CYP3A4 metabolic ratio and phenotype
- Pgp AUC and phenotype
- Venlafaxine concentration
- ODV concentration

Visit V2 and visit V3

- **Date of visits**
- Venlafaxine dose
- Other treatments: treatment 1, treatment 2 etc…
- MARS score
- MADRS score
- HAM-D score
- QIDS score
- PRISE-M score
- FISBER score

8.3 Right to access source data and documents

8.3.1 Access to data

In accordance with GCPs:

- The sponsor is responsible for obtaining the permission of all parties involved in the research to guarantee direct access to all locations where the research will be carried out, to the source data, to the source documents and the reports, with the goal of quality control and audit by the sponsor
- The investigators will make available to those in charge of monitoring, quality control and audit relating to the biomedical research the documents and personal data strictly necessary for these controls, in accordance with the legislative and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

8.3.2 Source documents

Source documents are defined as any original document or object that can prove the existence or accuracy of a piece of information or a fact recorded during theresearch. These documents will be kept for 15 years by the investigator or by the hospital in the case of a hospital medical file.

8.3.3 Data confidentiality

Those responsible for biomedical research quality control (Article L.1121-3 of the French Public Health Code) will take all necessary precautions to ensure the confidentiality of

information about the medications, the research, the research subjects and in particular the identity of the subjects and the results obtained.
These individuals, as well as the investigators themselves, are subject to professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the Penal Code).
During or after the biomedical research, the data collected about the research subjects and sent to the sponsor by the investigators (or any other specialised parties) will be made non-identifying.
Under no circumstances should the names and addresses of the subjects involved be shown.
The sponsor will ensure that each research subject has given permission in writing for access to personal information about him or her which is strictly necessary for the quality control of the research.

8.4 Data processing and storage of documents and data

8.4.1 Data entry

Data will be entered by staff dedicated to this task via duplicate data entry in forms for collecting anonymised data, in the Statistical Team of Saint Louis hospital, Paris (France).

8.4.2 Data processing (CNIL, the French Data Protection Authority) in France

This research falls under the "Méthodologie de référence" (MR-001) according to the provisions of Article 54, paragraph 5 of modified Law No. 78-17 of 6 January 1978 relating to information technology, data files and privacy. This change was approved in a decision made on 5 January 2006. AP-HP, the research sponsor, has signed a commitment to comply with this " Méthodologie de référence "

8.4.3 Archival

Specific documents for biomedical research relating to a medication for human use will be archived by the investigator and the sponsor for a period of 15 years after the end of the research.
This indexed archival includes, in particular:

- A sealed envelope containing the original copies of all information sheets and consent forms signed for all individuals at the center that participated in the research for the investigator
- A copy of all the information notes and consent forms signed for all subjects at the center that participated in the research for the sponsor
- "Research" binders for the Investigator and the sponsor, including:
- the successive versions of the protocol (identified by the version no. and date), and the appendices
- the ANSM authorisations and CPP favourable opinions
- letters of correspondence
- the inclusion list or register
- the appendices specific to the research
- the final research report
- The data collection documents

8.5 Ownership of the data

AP-HP is the owner of the data, which cannot be used or disclosed to a third party without its prior approval.

9 STATISTICAL ASPECTS

9.1 Description of statistical methods to be used

The statistical analysis will be performed once the sample size has been reached, and all the end point measures available.

9.2 Calculation hypotheses for the number of subjects required and the result

Remission rates with citalopram as the first step in STAR*D study were 28 to 33 per cent, and response rates averaged 47 per cent[12] after 14 weeks of treatment. After unsuccessful treatment with an SSRI, 28% of patients had a remission of symptoms after switching to V after 14 weeks of treatment. Schweitzer et al. observed, in patients suffering for moderate depression (MADRS=32.8 at entry) that 69% were responders to V after 8 weeks of treatment and 36.7% were in remission. Hence, the proportion of remitters and responders vary according to the study; the prevalence of responders is higher than remitters and the time to assess these criteria also vary according these studies. Schweitzeir et al. showed that in patients responders to V at 8 weeks, the response was maintained and even improved up to 10 months after[56]. Moreover, it is recognized that the antidepressant should be administered for 4 to 6 weeks before nonresponse can be assumed[11].

Given these date we estimate that response rates to V at 8 weeks will be 40%.

Our hypothesis is that the prevalence of patients with a CYP2C19 UM Metabolizer profile is twice as high in non-responders in comparison with responders, who have a CYP2C19 metabolic profile comparable to that of Caucasians (20%). To demonstrate that the prevalence is two-fold that observed in non-responders, with a type I error at 0.05 and a statistical power of 80%, the sample size is tabulated below according to the prevalence of response (**Table 17**).

Table 17: Computation of sample size

Expected prevalence of responders	Number of responders	Number of non responders	Total sample size
50%	82	82	164
33%	63	125	188
28%	59	146	205

Thus, to anticipate for potential large disproportion in responders/non responders (that will be only defined after study inclusion) we decided to include **205 patients**. This will allow to control for type I and type II error rates in the comparison of the prevalence of CYP2C19 Ultra-rapid Metabolizer profile among these groups.

In addition the sample size will allow to study sufficient numbers of CYP2D6 PM, IM, and UM to determine the effects of CYP2D6 variations on V and ODV plasma levels and their efficacy or risk of adverse events.

9.3 Anticipated level of statistical significance

The type I error rate will be fixed at 0.05. All tests will be two-sided and compared thus to 0.05.

9.4 Method for taking into account missing, unused or invalid data

Multiple imputation, which is a popular approach for handling the pervasive problem of missing data in biostatistics, will be used[102]. It is usually performed under a missing at random (MAR) assumption[103]. Multiple imputation by chained equation is to our knowledge the most flexible approach to handle complex patterns of missing data (including categorical data, quantitative data, and survival data).

9.5 Management of modifications made to the analysis plan for the initial strategy.

All modifications will be submitted for approval to the CPP.

9.6 Selection of populations

Primary analyses will be performed on an intent-to-treat basis.
Secondary exploratory analyses will consider the population of compliers, that is, those who completed the treatment according to the scheduled protocol.

10 QUALITY CONTROL AND ASSURANCE

Each biomedical research project managed by AP-HP is ranked from A to D according to the projected risk incurred by research subjects using the classification of biomedical research sponsored by AP-HP.

10.1 General organisation

The sponsor must be responsible for the safety and respect of those subjects who have agreed to participate in the research. The sponsor must implement a quality assurance system to best monitor the conduct of the research in the investigation centers.

For this purpose, the sponsor shall delegate Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the research locations, after having carried out initial visits.
The objectives of monitoring the research, as defined in the French Good Clinical Practices (BPC section 5.18.1), are to verify that:

- the rights, safety and protection of the research subjects are met
- the data reported is exact, complete and consistent with the source documents
- the research is carried out in accordance with the protocol in force, with the French GCPs and with the legislative and regulatory provisions in force

10.1.1 Strategy for opening the centers

The strategy for opening the centers established for this research is determined using the appropriate monitoring plan.

10.1.2 Level of center monitoring

In the case of this research, which is consideredat low risk, the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the research.

Thus, the sponsor and the coordinating investigator have agreed on the logistic score and impact, resulting in a research monitoring level to be implemented: level.

10.2 Quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the proper conduct of the research, for collecting and documenting, recording and reporting the data generated in writing, in accordance with the Standard Operating Procedures applied within the DRCD and in accordance with the French Good Clinical Practices as well as with the legislative and regulatory provisions in force.

The investigator and the members of the investigator's team agree to make themselves available during Quality Control visits carried out at regular intervals by the Clinical Research Associate. During these visits, the following elements will be reviewed:

- written consent
- compliance with the research protocol and with the procedures defined therein
- quality of the data collected in the case report form: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.)
- management of the treatments used

10.3 Case Report Form

All information required under the protocol must be entered in the case report forms and an explanation must be given for all missing data. The data must be collected as and when they are obtained, and must be clearly and legibly transcribed.
Erroneous data found in the case report forms will be stricken and the new data will be provided, next to the stricken data, initialled, with the date and, when applicable, with a justification from the investigator or the authorised individual who made the correction.

10.4 Management of non-compliances

Any events that occur as a result of non-compliance, by the investigator or any other individual involved in conducting the research, with the protocol, with the standard operating procedures, with the good clinical practices or with the legislative and regulatory provisions in force must be noted in a declaration of non-compliance addressed to the sponsor. As a first step, major or critical non-compliances will be reviewed and processed by the DRCD's medical coordinator in order to implement the necessary corrective or preventive actions. Next, the non-compliances will be sent to the Quality - Risk Management Division of the DRCD for verification and analysis. These verifications could result in the investigator in charge of the research location in question being asked for information or could lead to compliance or audit visits.

10.5 Audits/inspections

The investigators agree to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. Medical secrecy cannot be invoked in opposition to these audits and inspections.
An audit can be carried out at any time by individuals appointed by the sponsor and who are not associated with the research directors. The objective of the audit is to ensure the quality

of the research, the validity of the results and compliance with the legislation and regulations in force.
The individuals who lead and monitor the research agree to comply with the sponsor's requirements and with the competent authority regarding research audits or inspections.
The audit may be applicable to all stages of the research, from the development of the protocol to the publication of the results and the organisation of the data used or produced as part of the research.

10.6 Primary investigator's commitment to assume responsibility

Before starting the research, each investigator will give the sponsor's representative a copy of his/her personal curriculum vitæ, signed and dated, with his/her number in the RPPS (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals).
Each investigator will undertake to comply with the legislation and to carry out the research according to French GCP, adhering to the Declaration of Helsinki terms in force.
The primary investigator at each participating center will sign a responsibility commitment (standard DRCD document) which will be sent to the sponsor's representative.
The investigators and their employees will sign a delegation of duties form specifying each person's role.

10.7 Pharmacist's commitment to assume responsibility

The Clinical Trial Department of EP-HP, AGEPS, will be in charge of purchase, labeling and shipping of the drugs cocktail to the pharmacies of each center.

11 ETHICAL AND LEGAL CONSIDERATIONS

11.1 Methods for obtaining information and consent from research participants

In accordance with Article L1122-1-1 of the French Public Health Code, no biomedical research can be carried out on a person without free and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of said Code.
The patient will be first informed during their usual follow-up of the study if they are selected by the psychiatrist responsible for the follow-up. Then he or she will receive oral and written information (note of information) by the psychiatrist and another consultation will be planned, usually planned 7 to 20 days after, given the severity of the symptoms (usual follow-up). In accordance with the follow-up of the patients who require an increased dosage of V, an ECG will be prescribed.
The free and informed consent, in writing, of the subject is obtained by the investigator, or by a doctor representing the investigator, before the inclusion of the subject in the research
The information sheet and a copy of the consent form, signed and dated by the research subject and by the investigator or the doctor representing the investigator, are given to the individual prior to his or her participation in the research.
The subject will be granted a reflection period of **7 to 20 days** between the time when the subject receives the information and the time when he or she signs the consent form.

During the next consultation, they will receive additional information if necessary, and if the patient presents the criteria for inclusion, and if he agrees, he will sign the consent and the Visit V1 will be planned.
In addition, the investigator will specify in the research participant's medical file the methods used for obtaining his or her consent as well as the methods used for providing information with the goal of obtaining their consent. The investigator will retain the original signed and dated copy of the subject's consent form.

11.2 Special case: Mention of the possibility for the investigator of withholding certain information relating to the diagnosis, as applicable, in accordance with paragraph 4 of Article L1122-1 of the French Public Health Code.

Not applicable

11.3 Subject prohibited from participating in another research or an exclusion period anticipated after the research, if applicable

The exclusion period specified for this is the duration of the study (until V3), as each participant will receive a financial compensation for having participated to the study (150 euros) that he will receive at the end of the study.

During this period, the subject may participate in other biomedical research protocols relating to medications, but only non-interventional studies. In particular the patients can be included in the FondaMental Network for TRD.

11.4 Registration on the national register of subjects participating in biomedical research relating to the products listed in Article L. 5311-1 of the French Public Health Code

This step will be performed by each CIC after having received the fax of inclusion of the patient, in order to verify they have not been included in another protocol with financial compensation.
Itf they have been included in another protocol, they will be excluded and replaced by another patient.

11.5 Legal obligations

11.5.1 The sponsor's role

Assistance Publique - Hôpitaux de Paris (AP-HP) is the sponsor of this research and by delegation, the Clinical Research and Development Department (DRCD) carries out the research's missions in accordance with Article L.1121-1 of the French Public Health Code. Assistance Publique - Hôpitaux de Paris reserves the right to halt the research at any time for medical or administrative reasons. In this case, notification will be sent to the investigator

11.5.2 Request for an opinion from the Comité de Protection des Personnes (CPP, ethical review board)

AP-HP, as sponsor, obtains for this biomedical research relating to a medication for human use and prior to starting the research, the favourable opinion of the appropriate CPP, within

the scope of its authority and in accordance with the legislative and regulatory provisions in force.

11.5.3 Request for authorisation to ANSM

AP-HP, as sponsor, obtains for this biomedical research relating to a medication for human use and prior to starting the research, authorisation from the ANSM, within the scope of its authority and in accordance with the legislative and regulatory provisions in force.

11.5.4 Commitment to compliance with the MR 001 "Méthodologie de Reference"

AP-HP, the research sponsor, has signed a commitment to comply with this "Méthodologie de reference".

11.5.5 Modifications to the research

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, prior to starting the research, a favourable opinion from the CPP and authorisation from the ANSM within the scope of their respective authorities.
The information sheet and the consent form can be revised if necessary, in particular if there is a substantial modification to the research or if adverse reactions occur.

11.5.6 Final research report

The final biomedical research report referred to in Article R1123-60 of the French Public Health Code is drawn up and signed by the sponsor and the investigator. A summary of the report written according to the competent authority's reference plan will need to be sent to the competent authority and ethical review board within one year after the end of the research, meaning the end of the participation of the last research subject.

12 FUNDING AND INSURANCE

12.1 Funding source

This project is funded by the PHRC.
The dosages of drugs and their respective metabolites will be funded by the department of Pharmacology and Toxicology (Geneva). It represents 250 euros by patient.

12.2 Insurance

For the duration of the research, the Sponsor will take out an insurance policy covering the sponsor's own civil liability as well as the civil liability of all the doctors involved in carrying out the research. The sponsor will also provide full compensation for all harmful consequences of the research for the research subjects and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any agent. The act of a third party or the voluntary withdrawal of the person who initially consented to participate in the research cannot be invoked against said compensation.

Assistance Publique- Hôpitaux de Paris (AP-HP) has taken out insurance from HDI-GERLING through BIOMEDIC-INSURE for the full research period, covering its own civil liability and that of any agent (doctor or research staff), in accordance with Article L.1121-10 of the French Public Health Code.

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14 APPENDIX 1 : FORMULAIRE DE NOTIFICATION D'UN EVENEMENT INDESIRABLE GRAVE (EIG)

Direction de la Politique Médicale (DPM) Département de la Recherche Clinique et du Développement (DRCD)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS **Formulaire de notification d'un Evènement Indésirable Grave (EIG) survenant au cours d'une Recherche Biomédicale portant sur un Médicament ou produit assimilé**	**PARTIE RESERVEE AU PROMOTEUR** **REFERENCE VIGILANCE :** Référence GED : REC-DTYP-0192

Dès la prise de connaissance de l'EIG par l'investigateur, ce formulaire doit être dûment complété (3 pages), signé et retourné sans délai au pôle Vigilance du DRCD-Siège par télécopie au +33 (0)1 44 84 17 99

Notification initiale ☐ **Suivi d'EIG** ☐ **N° du suivi** |__|__|

1. Identification de la recherche

Acronyme : MARVEL

Code de la Recherche : P140562
Autre référence : EUDRACT No.: 2015-001139-19

Titre complet de la Recherche Biomédicale:
Exploration de la variabilité pharmacocinétique de la Venlafaxine par une approche phénotypique

Date de notification : |__|__| |__|__| |2|0|__|__|
jj mm aaaa

Date de prise de connaissance de l'EIG par l'investigateur : |__|__| |__|__| |2|0|__|__|
jj mm aaaa

Risque : ☐ A ☒ B ☐ C ☐ D

Plan expérimental : ☒ Essai non comparatif
☐ Essai comparatif : ☐ Double aveugle ☐ Simple aveugle ☐ Ouvert ☐ Randomisé ☐ Non randomisé

2. Centre Investigateur

Nom de l'établissement : .....
Ville et code postal : .....
Service : .....

Investigateur (nom/prénom) : .....
Tél : ..... Fax : .....

3. Identification et antécédents de la personne se prêtant à la recherche

Référence de la personne : |__|__|__| - |__|__|__|__|__| - |__| - |__|
n°centre - n° d'inclusion - initiale nom - initiale prénom

Sexe : ☐ M ☐ F

Poids : |__|__|__| kg
Taille : |__|__|__| cm

Date de naissance :
|__|__| |__|__| |__|__|__|__|
jj mm aaaa

Age : |__|__|__|ans

Date de signature du consentement : |__|__| |__|__| |2|0|__|__|
jj mm aaaa

Date d'inclusion : |__|__| |__|__| |2|0|__|__|
jj mm aaaa

Antécédents médicaux-chirurgicaux/familiaux pertinents pour l'évaluation du cas (joindre un CRH anonymisé le cas échéant) :
.....
.....
.....
.....
.....
.....
.....

Date de l'initiation de la Venlafaxine : |__|__| |__|__| |2|0|__|__|
jj mm aaaa

Date de majoration de la Venlafaxine : |__|__| |__|__| |2|0|__|__|
jj mm aaaa

4. Médicaments administrés dans le cadre de la recherche à la Visite V1, avant la survenue de l'EIG [médicaments non expérimentaux mais nécessaires à la réalisation de la recherche] : Date de la visite V1 : |__|__| |__|__| |2|0|__|__|

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie[1]	Posologie / jour	Heure de début *(jj/mm/aaaa)*	En cours[2]	Heure de fin *(jj/mm/aaaa)*
Omeprazole	.....	.....	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|
Midazolam	.....	.....	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|
Fexofenadine	.....	.....	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|
Dextrométhorphane	.....	.....	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|

5. Venlafaxine administrée pour le traitement de la dépression :

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie[1]	Posologie / jour	Date de début *(jj/mm/aaaa)*	En cours[2]	Date de fin *(jj/mm/aaaa)*
Venlafaxine : préciser spécialité	.....	.....	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|
Venlafaxine : préciser spécialité	.....	.....	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|
Venlafaxine : préciser spécialité	.....	.....	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|

Acronyme : MARVEL

Référence de la personne se prêtant à la recherche : |__|__|__| - |__|__|__|__|__| - |__| - |__|
n°centre - n° d'inclusion - initiale nom - initiale prénom

PARTIE RESERVEE AU PROMOTEUR

REFERENCE VIGILANCE :

Référence GED : REC-DTYP-0192

6. Médicament(s) concomitant(s) au moment de l'EIG, à l'exclusion de ceux utilisés pour traiter l'événement indésirable

(compléter le tableau ci-après et si nécessaire l'annexe relative aux médicaments concomitants ➾ **Annexe jointe au présent formulaire :** ☐ Oui ☐ Non *ou barrer l'encadré si non applicable) :*

Nom commercial (de préférence) ou Dénomination Commune Internationale y compris forme pharmaceutique et dosage	Indication	Voie[1]	Posologie / jour	Date de début *(jj/mm/aaaa)*	En cours[2]	Date de fin *(jj/mm/aaaa)*
....	....	....	....	|__|__| |__|__| |__|__|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
....	....	....	....	|__|__| |__|__| |__|__|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
....	....	....	....	|__|__| |__|__| |__|__|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
....	....	....	....	|__|__| |__|__| |__|__|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser) (2) En cours au moment de la survenue de l'EIG

7. Evènement indésirable grave [EIG]

Diagnostic : ☐ Définitif ☐ Provisoire
....
....

Organe(s) concerné(s) :
....
....

Symptôme(s) :
....
....

Date de survenue des premiers symptômes : |__|__| |__|__| |_2_|_0_|__|__|
Préciser lesquels ....
....

Date d'apparition de l'EIG :
|__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa
Heure de survenue : |__||__| hh |__||__| min
☐ *donnée manquante*

Délai entre la date de la dernière administration du ME/produit assimilé ou la date de procédure/acte ajouté par la recherche et la date de survenue de l'EIG :
|__||__| / |__||__| |__||__|
jj hh min

Critères de gravité :
☐ Nécessite ou prolonge l'hospitalisation :
du |__|__| |__|__| |_2_|_0_|__|__|
au |__|__| |__|__| |_2_|_0_|__|__| ☐ *en cours*
☐ Décès
☐ Mise en jeu du pronostic vital
☐ Incapacité ou handicap important ou durable
☐ Anomalie ou malformation congénitale
☐ Autre(s) critère(s) médicalement significatif(s), préciser :
....

L'évènement a-t-il conduit à une interruption du/des ME/produit assimilé(s) à l'étude ?
☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__|
L'arrêt de traitement a été : ○ Provisoire ○ Définitif
Le cas échéant, date de reprise du traitement à l'étude : |__|__| |__|__| |_2_|_0_|__|__|
Récidive de l'EIG après ré-administration : ○ Non ○ Oui - Date : |__|__| |__|__| |_2_|_0_|__|__|

L'évènement fait-il suite à :
-Une erreur médicamenteuse ? ☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__|
-Un surdosage ? ☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__|
-Un mésusage ? ☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__|
-Autre (préciser) : ☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__|

Degré de sévérité :
☐ Léger ☐ Modéré ☐ Sévère

Evolution de l'événement

☐ **Décès** Date : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa
○ sans relation avec l'EIG
○ en relation avec l'EIG

☐ **Sujet non encore rétabli**, préciser : ○ Etat stable ○ Aggravation ○ Amélioration

☐ **Guérison :** Date : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa
○ sans séquelles
○ avec séquelles, préciser lesquelles :
....
|__|__| |__|__|
hh min

Des mesures symptomatiques ont été prises :
☐ Non ☐ Oui Si oui, préciser : ....
....

8. Autre(s) étiologie(s) envisagée(s) :

☐ Non ☐ Oui Si oui, préciser : ....
....
....

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PARTIE RESERVEE AU PROMOTEUR

REFERENCE VIGILANCE :

Référence GED : REC-DTYP-0192

9. Examen(s) complémentaire(s) réalisé(s) :

☐ Non ☐ Oui Si oui, préciser date, nature et résultats : [joindre les bilans anonymisés].....

.....

.....

.....

10. Selon l'investigateur, l'événement indésirable grave est (plusieurs cases possibles) :

Lié à la recherche biomédicale :

☐ Oui : ○ **au(x) médicament(s) de la recherche (non expérimentaux mais nécessaires à la réalisation de la recherche : procédure de la recherche)**

- **venlafaxine** ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable
- **oméprazole** ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable
- **midazolam** ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable
- **dextromorphane** ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable
- **fexofenadine** ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable

☐ **Non** : ○ **à la progression de la maladie faisant l'objet de la recherche :** dépression
○ **à un (ou plusieurs) médicament(s) concomitant(s) administré(s), le(s)quel(s) :** .....
○ **à une maladie intercurrente, laquelle :** .....
○ **autre, préciser :**

Notificateur	**Investigateur**	Tampon du service :
Nom et fonction :	Nom :	
Signature :	Signature :	

Direction de l'Organisation Médicale et des relations avec les Universités (DOMU)

Département de la Recherche Clinique et du Développement (DRCD)

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Liste relative aux médicaments concomitants utilisés dans le cadre d'une recherche biomédicale : Annexe au formulaire de notification d'un Evènement Indésirable Grave (EIG)

PARTIE RESERVEE AU PROMOTEUR
REFERENCE VIGILANCE :

Dès la prise de connaissance de l'EIG par l'investigateur, ce document doit être dûment complété, signé et retourné sans délai au pôle Vigilance du DRCD-Siège par télécopie au +33 (0)1 44 84 17 99 avec le formulaire de notification d'EIG complété

Notification initiale ☐ **Suivi d'EIG** ☐ **N° du suivi** |__|__|

Acronyme : MARVEL

Référence de la personne se prêtant à la recherche : |__|__|__| - |__|__|__|__| - |__| - |__|
n° centre - n° d'inclusion - initiale nom - initiale prénom

Investigateur (nom/prénom) : ……………………

Service : …………… Tél. : …………… Fax : ……………

REPORTER TOUS LES MEDICAMENTS CONCOMITANTS AU MOMENT DE L'EIG, A L'EXCLUSION DE CEUX UTILISES POUR TRAITER L'EVENEMENT INDESIRABLE :

Nom commercial (de préférence) ou Dénomination Commune Internationale y compris forme pharmaceutique et dosage	Indication	Voie(1)	Posologie / jour	Date de début (jj/mm/aaaa)	En cours(2)	Date de fin (jj/mm/aaaa)
……………	……………	……	……	|__|__| |__|__| |__|__|__|__|	☐	|__|__| |__|__| |2|0|__|__|
……………	……………	……	……	|__|__| |__|__| |__|__|__|__|	☐	|__|__| |__|__| |2|0|__|__|
……………	……………	……	……	|__|__| |__|__| |__|__|__|__|	☐	|__|__| |__|__| |2|0|__|__|
……………	……………	……	……	|__|__| |__|__| |__|__|__|__|	☐	|__|__| |__|__| |2|0|__|__|
……………	……………	……	……	|__|__| |__|__| |__|__|__|__|	☐	|__|__| |__|__| |2|0|__|__|
……………	……………	……	……	|__|__| |__|__| |__|__|__|__|	☐	|__|__| |__|__| |2|0|__|__|
……………	……………	……	……	|__|__| |__|__| |__|__|__|__|	☐	|__|__| |__|__| |2|0|__|__|
……………	……………	……	……	|__|__| |__|__| |__|__|__|__|	☐	|__|__| |__|__| |2|0|__|__|
……………	……………	……	……	|__|__| |__|__| |__|__|__|__|	☐	|__|__| |__|__| |2|0|__|__|
……………	……………	……	……	|__|__| |__|__| |__|__|__|__|	☐	|__|__| |__|__| |2|0|__|__|
……………	……………	……	……	|__|__| |__|__| |__|__|__|__|	☐	|__|__| |__|__| |2|0|__|__|

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser) (2) En cours au moment de la survenue de l'EIG

Notificateur	Investigateur	Tampon du service :
Nom et fonction :	Nom :	
Signature :	Signature :	