LFB BIOMEDICAMENTS
3, AVENUE DES TROPIQUES, LES ULIS - BP 40305 - 91958 COURTABOEUF CEDEX – FRANCE

SYNOPSIS

WiSH-QoL
VWD Quality of Life

TITLE	Quality of Life study and health-economic assessment in patients with Von Willebrand Disease in France
SPONSOR	LFB BIOMEDICAMENTS 3, Avenue des Tropiques BP 40305 91958 COURTABŒUF Cedex, France
COORDINATOR	Dr Annie BOREL-DERLON (Caen, France)
STEERING COMMITTEE	Dr Annie BOREL-DERLON (Caen, France) Dr Edith FRESSINAUD (Lille, France) Pr Jenny GOUDEMAND (Lille, France) Pr Agnès VEYRADIER (Paris, France) PR Yohann REPESSE (Caen, France) PR Sophie SUSEN (Lille, France) Dr Sylvia Von MACKENSEN (Hambourg, Allemagne)
INVESTIGATIONAL THERAPIES / MEDICINAL PRODUCTS	All Von Willebrand Disease treatments: - medicinal products such as desmopressin, tranexamic acid, … - replacement therapy with human Von Willebrand Factor (WILFACTIN®, WILSTART®), - other concomitant medicinal products..., - procedures...
STUDY CHARACTERISTICS	Prospective, uncontrolled, observational, non-interventional, descriptive, multicentre study without modification of the doctor-patient relationship in France. No additional diagnostic or monitoring procedure will be required.

PRIMARY OBJECTIVE	Analyse the quality of life of patients with Von Willebrand Disease using generic and Von Willebrand Disease-specific quality of life questionnaires.
SECONDARY OBJECTIVES	**1.** Survey and identify therapeutic practices in Von Willebrand Disease 1.a. Evaluate treatment consumption by follow-up period in all situations treated. 1.b. Evaluate and compare bleeding scores observed at inclusion (M0) and after 24 months of follow-up (M24). 1.c. Evaluate the efficacy of long-term prophylaxis (LTP) on the frequency of bleeds. 1.d. Identify and survey practices in the biological monitoring of replacement therapy with VWF. 1.e. Evaluate the safety of WILFACTIN®, WILSTART® in all situations treated. **2.** Evaluate the impact of treatment strategies on Von Willebrand Disease. **3.** Investigate/analyse the impact of Von Willebrand Disease on the clinical status, treatments and complications in subgroups of the population A. Women of childbearing age B. Patients with gastrointestinal (GI) bleeds C. Patients with joint bleeds D. Patients with Ear-Nose-Throat (ENT) / stomatology bleeds (excluding those connected with surgery) **4.** Evaluate the health-economic impact of Von Willebrand Disease.
PATIENT COHORT	About 350 patients with Von Willebrand Disease
POPULATION STUDIED (Eligibility criteria)	▪ Inclusion criteria Male or female patients of any age with congenital Von Willebrand Disease, with a phenotype suggesting type 1 (restricted to those with trough VWF:Ag < 30%), type 2 or type 3, and who are seen in a Treatment Centre in France. Having signed and dated informed consent form.

	▪ Non-inclusion criteria - Acquired Von Willebrand Syndrome - Any other haemostatic disorder associated with a bleeding risk - Inability of the patient to follow study recommendations (for example, inability to fill out the quality of life questionnaire).
DURATION OF PATIENT PARTICIPATION	▪ Estimated at 24 months for participation and follow-up (- 3 months to + 6 months). The study will be conducted without modifying the doctor-patient relationship in conditions of common medical practice, without any additional diagnostic or monitoring procedure. The schedule of patient consultations or visits to the hospital cannot be determined in advance and depends on each patient. The visit made the closest to the date of inclusion plus 24 months will be the date used as the end-of-study date, unless there is an early withdrawal.
STUDY START DATE AND END DATE	Provisional study start date: 1st patient included - Q4 2013 Provisional study end date: last patient completed - Q4 2019
STUDY DESCRIPTION	• Selection of centres The study will be proposed to Haemophilia and VWD treatment centres and to any other practitioner who autonomously cares for patients in France. • Inclusion of patients Once the centre is open, the participating doctor must provide each patient who comes in for a consultation or hospitalisation and who meets the criteria for participation (and/or his/her parents/legal guardian/family member/trusted person) with complete relevant information in writing and orally about the objectives of the study and the procedures involved. The information sheet provided will comply with the French data privacy law no. 78-17 of 6 January 1978, as amended. If possible, the patient (and/or his/her legal guardian) must be given enough time to think his/her participation over and ask for further information about the study. After presentation of the study, the patient will be asked to agree to participate in the study and consent to his/her data being viewed by a representative of the Sponsor. The signed informed consent form must be obtained from the patient (and/or his/her legal guardian) before any study-related procedure can be performed: record of study data. The information sheet also states that the overall results will be provided to the patient at the end of this study if he/she wishes.

	• Data collection and Monitoring Collection of data by the participating doctor, in accordance with the Protocol, in an electronic case report form. To facilitate completion of the study and if the participating doctor wishes, an independent Clinical Trial Technician will be appointed to help enter the data into the case report form. The participating doctor will complete the medical sections for which he/she is responsible, and will validate all of the data recorded into the case report form. The monitoring will be performed by monitors (clinical research associates) of a Contract Research Organisation that was not involved in collection of the data. • Biometrics and study report The data management and statistical analyses will be performed and the statistical reports will be written by one or more contract service providers specialised in the areas of quality of life and health-economics.
DESCRIPTION OF AND JUSTIFICATION FOR THE DATA COLLECTED	**Nominal data** Nominal data such as date of birth in complete format (day/month/year) and patient initials will be recorded at inclusion so that any data concerning the patient collected later if he/she is monitored at several sites can be attributed to that same patient. The participating doctors will note in the case report form whether or not the patient is participating in the registry of the Von Willebrand Disease Reference Centre: CRMW. The patients will need to be identified so that they can be accurately monitored and to allow for quality control of the data and comparison with the source data, including those included in the CRMW registry. The data will be collected when available from the medical file (including the injection journal) and the patient "diary", in order to gather the data and information required by the Protocol. **Quality of life questionnaires** Quality of life will be evaluated using self quality of life questionnaires completed by the patients. The generic questionnaires used will be: – SF-36 for adults, – Disabkids for the quality of life of children and adolescents: ▪ version for children aged 4-7 years, ▪ version for adolescents aged 8-17 years ▪ and the corresponding versions for parents.

	– The FABEL questionnaire (Der Familien-Belastungs-Fragebogen) evaluates the consequences of chronic pathologies or disabilities during childhood and adolescence. It will be used to measure the impact on the family for all children between 0 and 17 years of age. The specific quality of life tool will be the VWD-specific QoL instrument which includes Treatment Satisfaction in all of its versions: adults, children aged 4-7 years, adolescents aged 8-17 years and corresponding versions for parents, including that for very young children under 4 years of age. These Questionnaires will be administered at inclusion (M0) and after 24 months of follow-up (M24). **The diary for the patient** Suitable questionnaires designed specifically for the study will be given to the patients to collect sociodemographic data and information on the costs and needs connected with their disease. They will be given a diary to help them answer these questions. **Joint score** For patients who only have joint symptoms, the joint score will be measured at inclusion and after 24 months of follow-up, using Gilbert's score. *(*[30] **Gilbert MS**. Semin Hematol 30 (3 Suppl 2):3-6, 1993*)*. A visual analogue pain scale will also be used at inclusion (M0) and after 12 and 24 months of follow-up (M12 and M24). These analogue pain scales will only be used in cases of joint pain and not for gynaecological pain which is not comparable. **Bleeding score** For each patient regardless of their age, the frequency and severity of bleeds and their conditions of onset will be recorded and the factors affecting their severity will be studied through calculation of the standardised bleeding score (with 12 items rated from -1 to 4) ([13] **Tosetto A.** J Thromb Haemost 2006;4:766–73). This score will be measured at inclusion (M0) and after 24 months of follow-up (M24). In addition to the calculated score described above, two series of questions from the International Society on Thrombosis and Haemostasis (ISTH) score will be added to the case report form. These are questions 9 and 10 on postpartum haemorrhages and menorrhagia from the "ISTH/SSC Bleeding Assessment Tool: A Standardized Questionnaire and a Proposal for a New Bleeding Score for Inherited Bleeding Disorders, ([14] **Rodeghiero F,** ISTH/SSC bleeding assessment tool: a standardized questionnaire and a proposal

	for a new bleeding score for inherited bleeding disorders. J Thromb Haemost 2010; 8: 2063–5). They will also be evaluated at inclusion (M0) and after 24 months of follow-up (M24). **Biological results** The biological results for VWF:RCo, VWF:Ag, FVIII:C, platelet count and red blood cell and haemoglobin levels will be reported when available. The type of genetic defect will also be given if it is known. Clinical and biological data (hepatitis A and B vaccination, viral status and VWF inhibitor history) will be reported.
ENDPOINTS AND PARAMETERS	1. **For the analysis of quality of life,** the quality of life information collected at inclusion and at 24 months of follow-up will be analysed by the "scoring" methodologies in each questionnaire used: generic quality of life questionnaire for adults and for children/parents and Von Willebrand Disease-specific questionnaires, including treatment satisfaction. The difference between the quality of life scores obtained at inclusion (M0) and at the end of follow-up (M24) will be evaluated. The quality of life tools selected for this study are specific to the patient's age (young child / child / adolescent / adult). If the age group changes during the study, it was decided to keep the version of the questionnaire used the 1st time at inclusion. 2. **The Survey and identification of therapeutic practices** in Von Willebrand Disease will cover several parameters: 2.a. The evaluation of consumption of the various therapeutic options will be based on analysis of the number of units injected, of injections and treatment days, and on the type and number of situations treated (minor and major bleeding episodes, surgical procedures including rehabilitation, prophylaxis) per follow-up period. The use of other therapies with the replacement treatment with Von Willebrand Factor will also be evaluated. 2.b. Analysis of the difference between bleeding scores measured at inclusion and at the end of the study (24 months). 2.c. The efficacy of prophylaxis will also be evaluated based on the frequency of bleeds before and during the period of long-

term prophylactic treatment. The number of bleeding episodes occurring under exclusively on-demand treatment will be estimated for the 12 months prior to the initiation of prophylaxis. This result will be compared with that obtained after a period which does or does not follow the initiation of LTP lasting at least 12 months.

2.d. The practices used for the biological monitoring of replacement treatment with VWF in order to adapt the posology will be identified and surveyed by analysing the types of dosages prescribed and the techniques and frequency of administration. This evaluation will be performed for episodes requiring hospitalisation.

2.e. The safety of replacement treatment with Von Willebrand Factor (WILFACTIN®/WILSTART®) in all situations treated will be evaluated by:

- analysing all adverse events reported by the patient,
- analysing all adverse events reported by the treating physician which occur during the treatment period,
- and determining whether any of these events could be related to the product.

3. **The outcome of the treatment strategies on Von Willebrand Disease** will be measured by type of Von Willebrand Disease and age group. It will be based on the long-term results of each strategy (on-demand *versus* prophylaxis) and on the differences between the quality of life scores measured at 2 time points.

4. **The impact of Von Willebrand Disease on the clinical manifestations, therapeutics and disease complications in subgroups of the population** will be analysed based on:

A. Women of childbearing age

4.a. The frequency of obstetrical and gynaecological problems in all types of Von Willebrand Disease,

4.a. Evaluation of the link between the phenotype and the clinical signs and their severity,

4.a. Evaluation of the various therapeutic options to reduce menorrhagia complications. Determination of the proportion of women requiring LTP.

4.a. Evaluation of the efficacy of LTP in women with menorrhagia.

B. Subgroup of patients with gastrointestinal (GI) bleeds
   - B.a. Evaluation of the various therapeutic options to reduce GI bleed complications. Determination of the proportion of patients requiring LTP.
   - B.b. Evaluation of the efficacy of LTP in these patients.

C. Subgroup of patients with joint involvement
   - C.a. Evaluation of the various therapeutic options to reduce hemarthrosis complications. Determination of the proportion of patients requiring LTP.
   - C.b. Evaluation of the efficacy of LTP in these patients.
   - C.c. Evaluation and comparison of the differences between joint scores (Gilbert's score) measured at inclusion and after 24 months of follow-up.
   - C.d. Evaluation and comparison of the differences between pain scores on the Visual Analogue Scale (VAS) at 3 time points: inclusion, M12 and M24.

D. Subgroup of patients with ENT / stomatology bleeds (excluding those connected with surgery)
   - D.a. The frequency of ENT bleeds in all types of Von Willebrand Disease.
   - D.b. Evaluation of the link between the phenotype and the clinical signs and their severity.
   - D.c. Evaluation of the various therapeutic options to reduce the complications of these bleeds. Determination of the proportion of patients requiring LTP.

5. The health-economic analysis will include a descriptive evaluation of the direct and indirect costs of health care consumption, and a comparison of the costs of the various treatment regimens (on-demand / prophylaxis). The annual costs of Von Willebrand Disease management in France, in terms of consumption of procedures, therapies and Von Willebrand Factor, as well as the indirect costs will be analysed. These costs will be estimated based on the rates of the system of payment per medical act implemented in France in 2004, in the version in force at the time of estimation of the resources consumed. The costs of replacement therapy with Von Willebrand Factor, which is not included in the activity fees schedule, will be estimated separately.

- **Direct medical costs**: estimated from the point of view of the third-party payer, calculated by multiplying the resources consumed over the follow-up period by their unit costs.

	- **Indirect medical costs**: absenteeism from school, work leaves, costs of childcare for child patients, financial subsidies, only estimated and presented descriptively. The population will be divided into 2 groups: - young children / children / school-aged adolescents, - adults.
STATISTICS	Two interim analyses are planned: - the first, performed at the end of the 1st year of inclusion. (planned for the 4th quarter of 2014) - the second, in Q4 2017 The final analysis is planned for 4 months after database freeze (estimated Q3 2021). The statistical analysis will be mainly descriptive for each endpoint. The quantitative variables will be expressed as a mean ± standard deviation, median, quartiles and range, and the qualitative variables will be expressed as a frequency table.
ETHICAL AND REGULATORY ISSUES	This non-interventional study will be conducted in accordance with current reference texts in force. - Guideline on good pharmacovigilance practices: Module VI – Management and reporting of adverse reactions to medicinal products, EMA, HMA, 22 June 2012 - Guide on Methodological Standards in Pharmacoepidemiology, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (**ENCePP**) - Revision 1, June 2012 - Guidelines for Good Pharmacoepidemiology Practices (**GPP**), International Society for Pharmacoepidemiology (ISPE), April 2007 - Good Epidemiological Practice (**GEP**), International Epidemiological Association (IEA), November 2007 - French data privacy law no. 78-17 of 6 January 1978, as amended (n°2004-801 on 6 august 2004 for the protection of individuals with regard to the processing of personal data). - International Conference on Harmonisation (ICH) topic E6 (CPMP/ICH/135/95). The study will be submitted to the Northwest III Committee for the Protection of Persons (CPP, ethics committee) of Caen, France. The Protocol and associated documents will be submitted to the Advisory Committee for the Treatment of Health Research Data (CCTIRS).

	Furthermore, the approval of the French Data Protection Committee (CNIL) will be required for automated processing of the nominative data collected for this study. In accordance with article L.4113-6 of the French Public Health Code as amended by the law of 18 January 1994, the Sponsor will request the opinion of the French National Board of Physicians (CNOM) on the Protocol and contracts of the participating doctors.