EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 October 2023
EMADOC-1700519818-1173599
Executive Director

Letter of Support for World Federation of Hemophilia (WFH) Gene Therapy Registry (GTR)

The World Federation of Hemophilia (WFH), in collaboration with the International Society of Thrombosis and Hemostasis (ISTH), the European Association for Haemophilia and Allied Disorders (EAHAD), the European Hemophilia Consortium (EHC), the US National Hemophilia Foundation (NHF), the American Thrombosis and Hemostasis Network (ATHN), industry gene therapy development partners and regulatory liaisons, has established the Gene Therapy Registry (GTR), a worldwide database intended to gather long-term, real-world data on all persons with hemophilia (PWH) who receive gene therapy.

The global reach of the GTR has, in principle, two advantages: it prevents the need for every gene therapy manufacturer and hemophilia treatment centre (HTC) to maintain separate patient registries to ascertain long-term outcomes. Moreover, given the low prevalence of the disease worldwide, it provides a central data repository that is more likely to detect low-incidence events and provides larger sample sizes of PWH to carry out more methodologically robust analyses. While such a disease registry is of particular value, the data collected could also serve to inform aspects on efficacy and safety in general through collaboration with registries for gene therapies.

The primary ***objective*** of the GTR is to determine the long-term *safety* of gene therapies to treat hemophilia A and B in PWH, e.g. identified hepatotoxicity with some gene therapy products, but also yet unknown safety issues that may be identified in the long term. The secondary objective of the GTR is to determine the long-term *efficacy* and *durability of activity* of factor VIII and factor IX with gene therapies in PWH.

The GTR has established a ***core dataset*** to meet its objectives of collecting long-term data on the safety and efficacy on gene therapies in PWH. Data fields included in this dataset were based on EMA recommendations for core data elements required for novel products used in the treatment of hemophilia, on earlier interactions between EMA and WFH regarding the GTR, and on FDA recommendations.

Any PWH who has received gene therapy, through a clinical trial, compassionate use, or as a product that has received market approval will be eligible for ***enrolment*** in the GTR. Clinical trial participants will be enrolled in the GTR either upon completion of the clinical trial, or earlier if permitted by the clinical trial protocol. There are no exclusion criteria for the GTR. PWH will be recruited through two approaches to allow worldwide enrolment: 1) directly via participating hemophilia treatment centres

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(HTCs); and 2) via data from existing gene therapy patient registries. Ideally, PWH will be enrolled in the GTR at the same time that they receive their gene therapy so that all relevant baseline and historical data required for GTR can be obtained. Patients may also enter after transfer of their data from other existing gene therapy registries (such as national registries).

The WFH has developed support programs, so called GTR Readiness Programs, for participating HTCs and participating PWH to ensure data and data entry are appropriately managed. The WFH GTR has a patient consent management program in place and also a process to de-identify patient health information. The platform is compliant with all privacy regulations (HIPPA, GDPR, CCPA). The GTR's ***governance*** structure includes a Steering Committee, a Scientific Advisory Board, an Industry Consortium, and a Patient Advisory Group.

The GTR Scientific Advisory Board has the right to publish periodic aggregate reports of data collected in the GTR (subject to any confidentiality requirements of industry partners) on the WFH website or other publicly accessible platforms. The Scientific Advisory Board also has the right to use data collected in the GTR to conduct scientific analyses and to disseminate the findings of these analyses through the grey literature, peer-review journals, or at scientific meetings or conferences. Each industry involved through their medicinal product will receive their ***product-specific data***, directly from the GTR, on a regular basis. Industry involved and third parties (e.g. academic research organisations) can make requests for access to global GTR data to conduct scientific studies based on a detailed research protocol. If the GTR Scientific Advisory Board approves the study proposal, a data sharing agreement will be established between the GTR, the relevant industry, and the data recipient(s).

The Committee for Medicinal Products for Human Use (CHMP) acknowledges that the GTR represents a novel method for ascertaining the long-term safety and efficacy of gene therapies in hemophilia, capturing important clinical and patient-derived information. Additionally, it may provide information on optimal dosing strategies, factors leading to development of immunogenicity, and underlying patient characteristics that predict success of therapy.

Data collected in the GTR could be used to inform regulatory decisions and health technology assessments (HTAs) of gene therapies in PWH. It may also contribute valuable information to clinical practice guidelines for the treatment of hemophilia, and to research and development of new therapies for this condition.

The full WFH GTR protocol (core dataset) is found in the ***Appendix***. It will be shared on the clinicaltrials.gov website and on EU electronic register of post-authorisation studies (EU PAS Register) before data collection begins. Overall, the variables collected are well aligned with EMA recommendations regarding evaluation of novel products used in the treatment of hemophilia and are in line with the core data set described in the Report on Haemophilia Registries Workshop held on 08 June 2018 (EMA/487643/2018) and the Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products (EMA/CHMP/BPWP/144533/2009 rev. 2). Data collected include baseline/infusion data, follow-up visits (safety/efficacy collected by physicians, bleeding history data and some information on quality of life directly collected by patients using an electronic patient engagement tool ('myGTR' application). A process is in place to add further variables to the database, which is appreciated but should foresee also retrospective addition of data for specific studies. Finally, reporting summary data only may be sufficient but in certain situations informed consent allows that raw data / individual line listings (including patient narratives) can be made available for analysis of, for example, safety issues.

With regard to data quality, i.e. accuracy and completeness, adequate systems are in place that seem appropriate for the intended use of the WFH GTR. To date, the GTR has worked with three national registries to ensure alignment of the core datasets: the American Thrombosis and Hemostasis Network

(ATHN) (USA), the Canadian Bleeding Disorders Registry (CBDR), and HemoNed (Netherlands). Datasets of other registries that collect data on gene therapy in PWH are currently being assessed for potential future collaborations. Minimum data requirements for collaboration with an existing registry should be defined and transparent.

To ensure long-term follow-up, a retention strategy for PWH and hemophilia treatment centres consisting of financial and social interaction seems reasonable. Approaches to analysing safety and efficacy data and reporting timelines seem all reasonable, but with some suggestions for clarification or improvement given in the Scientific Advice procedure (EMA/SA/0000106677).

Finally, the WFH GTR cannot be qualified at this stage since this will primarily depend on its demonstrated ability to collect and report data in the context of a study, which has yet to be established. It will be important to understand the feasibility of the proposed data collection to validate the quality and completeness of the data that is planned to be collected. The WFH GTR is considered a tool that may collect relevant data in a registry that could provide context and assure long-term follow-up. The collection of patient relevant data, in part collected directly from patients using 'myGTR', is considered an asset of the registry. Also, the structured collection of adverse events using MedDRA terminology is appreciated.

In conclusion, the CHMP supports the WFH GTR as the worldwide registry for consolidating all international data on individuals with hemophilia who receive gene therapy and encourages collaboration of hemophilia treatment centres and national registries worldwide. It is expected that utilising the WFH GTR for post approval safety or efficacy studies of gene therapies will be of particular value and its use as planned data source for mandated Phase IV studies for new hemophilia treatments is recommended.

The letter of support is issued on the basis of this qualification advice.

Yours sincerely,

Emer Cooke
Executive Director

Appendix

Gene Therapy
Updated Core Data Set - Data Fields
June 2023

Baseline
Baseline patient data is defined as the most recent data obtained before infusion (including past gene therapy patients)

Demographics, diagnosis, medical/clinical history

Data Field	Response field
Demographics	
Enrolment date	DD/MM/YYYY
Date of birth	DD/MM/YYYY
Sex at birth	Male Female
Country of residence	List of all countries
Race (multiselect)	White Black Asian Other, specify Unknown Not reported
HTC for GT administration	List of HTCs Other, specify
HTC for follow-up data	Same as HTC for GT administration List of HTCs Other HTC, specify
Diagnosis	
Hemophilia Type	A B
Severity	Mild Moderate Severe
Year of diagnosis (if known)	YYYY
DNA Variant	Intron 22 inversion Intron 1 inversion Other, please specify (using HGVS terminology) Not Done Unknown
DNA Variant type	Inversion Large structural variant (≥ 50 bp) Nonsense Frameshift Small insertion or deletion (indel) (<50 bp) Splice Missense Synonymous Promoter UTR Other, please specify Unknown
Factor Level at Diagnosis	
Factor level at diagnosis	Open field
Factor level units	%

	IU/dL
Date of factor level test	DD/MM/YYYY
Medical / Clinical History	
Family history of hemophilia	Yes No Unknown
Has the patient ever had a positive factor inhibitor?	Yes No Unknown
Does the patient currently have a factor inhibitor?	Yes No Unknown
Date of most recent titer result unit	DD/MM/YYYY
Type of most recent titer test	Bethesda Nijmegen-Bethesda Mixing study Unknown
Most recent titer result	Open field
Did the patient receive Immune Tolerance Induction (ITI)?	Yes No Unknown
What was the last treatment regime the patient was on prior to receiving GT?	Prophylaxis On demand Other, specify No treatment Unknown
What type of prophylaxis	Clotting factor concentrate Standard half-life Extended half-life Hemostatic rebalancing agent Please specify Bispecific antibodies Emicizumab Other, specify Other, specify
Approximately how many continuous years was the patient on this treatment regime prior to receiving gene therapy?	Open field (numeric, round numbers)
On demand treatment type	Extended half-life clotting factor concentrate Standard half-life clotting factor concentrate Other, specify
Approximately how many days of on demand treatment has the patient had in the past year prior to receiving gene therapy?	Open field (numeric, round numbers)
Number of exposure days of factor replacement therapy prior to gene therapy infusion?	None <50 days 50-150 days >150 days Unknown
AAV Neutralizing Antibodies to product received (prior to infusion)	
Test methodology	Transduction inhibition assay Total antibody Other, specify

Date of test	DD/MM/YYYY
Result	Positive Negative N/A
Titre (if recorded)	Open field
Pre-existing / co-morbidities (select all that apply)	
Thromboembolic event(s)	Yes No Unknown
Which event?	Deep vein thrombosis Myocardial infarction Pulmonary embolism Non-hemorrhagic stroke Thrombotic microangiopathy Other, specify
Date of onset	DD/MM/YYYY
Predisposing factor identified (check all that apply)	Hospitalization Major Surgery Major Trauma Cancer Immobility with travel for > 6 hours Family history of venous thrombosis Family history of heart disease or stroke Hypertension Dyslipidemia Diabetes Cigarette smoking Severe infection including COVID19 Hormonal therapy Obesity Other, specify
Autoimmune disorders	Yes No Unknown
Which autoimmune disorder?	Systemic lupus erythematosus Rheumatoid arthritis Psoriasis Ulcerative colitis Crohn's disease Multiple sclerosis Sjogren's syndrome Polymyalgia rheumatic Ankylosing spondylitis Type 1 diabetes Other (please specify)
History of cancer	Yes No Unknown
Type of cancer	Lymphoma Leukemia Liver Lung Prostate Colorectal Stomach

	Breast Other, specify
HIV-positive	Yes No Unknown
Has the patient developed new sensory disturbances?	Yes No Unknown
Please describe sensory disturbances	Tingling Numbness Pain not attributed to another cause (carpal tunnel, shingles, etc)? Other, specify
Liver-related medical history	
Pre-existing liver disease	Autoimmune hepatitis Fatty liver disease Gilbert's syndrome Other, specify
History of hepatitis C infection	Yes No Unknown
Infection resolved?	Ongoing Resolved
Date infection resolved	MM/YYYY
Estimated duration of Hep C infection to the nearest 10 years	Open field
History of hepatitis B infection	Yes No Unknown
Ongoing infection (HBsAg and/or HBV DNA positive)?	Yes No
Most recent liver assessment in the last 2 years	Liver ultrasound CT scan MRI Liver biopsy Fibrosis stage assessment ALT AST Total bilirubin Alpha fetoprotein
Date (most recent)	DD/MM/YYYY
Results (most recent)	Normal Abnormal, please explain
Result (most recent)	Open field
Result units	*Units*
Liver biopsy: Was a METAVIR score (activity grade) obtained?	Yes No
METAVIR score (Activity grade)	A0: no activity A1: mild activity A2: moderate activity A3: severe activity
Was a METAVIR score (fibrosis stage) obtained?	Yes No
METAVIR score (fibrosis stage)	F0: no fibrosis

	F1: portal fibrosis without septa F2: portal fibrosis with few septa F3: numerous septa without cirrhosis F4: Cirrhosis
Fibrosis stage methodology	Radiologic Serologic
Radiologic methodology	Fibroscan Other, specify
Score	Open field
Serologic methodology	Fibrotest/Fibrosure Hepascore FibroSpect ELF Score Other, specify
Score	Open field (numerical, 0-50, 2 decimals)
Concomitant medication	
Any concomitant medication (prescription, over the counter (OTC), herbal medications, and supplements)?	Yes No Unknown
Which medication	List of medications (incl. over the counter) Other, specify Unknown
Alcohol consumption	Yes No Unknown
Over the past month, on average how many drinks were consumed per week? (One drink equals one bottle of beer or cooler, 150 ml (5 oz) glass of wine, or any drink containing a shot of liquor)	0 1-3 4-7 8 or more

Gene Therapy Details

Data Field	Response field
Vector product – hemophilia A	Giroctocogene fitelparvovec (Pfizer, Sangamo SB-525) Valoctocogene roxaparvovec / Roctavian (Biomarin) Dirloctocogene samoparvovec (Spark SPK-8011) Other, specify
Vector product – hemophilia B	Etranacogene dezaparvovec (CSL Behring / uniQure) Fidanacogene elaparvovec (Pfizer, Spark SPK-9001) Verbrinacogene setparvovec (Freeline FLT180a) Other, specify
Product received as	Clinical trial product Commercial product
Clinical trial number	*All clinical trial numbers* Other, specify
Site ID number	Open field
Patient trial ID number	Open field
Batch number	Open field
Lot number	Open field
Date of infusion	DD/MM/YYYY
Dose – total vector genomes	Open field
Dose – total vector genomes - multiplier	x 10^{11} x 10^{12}

	x 10^{13} x 10^{14} x 10^{15}
Patient weight at dosing (kg)	Open field
Complications at time of infusion (24 hours)	Yes à pop up for AE entry No Unknown
Which complication(s)	Fever (>38.5) Myalgia Hypotension Rash Other, specify Unknown
Complications during the following 2 weeks	Yes à pop up for AE entry No
Which complication(s)	Fever (>38.5) Myalgia Hypotension Rash Other, specify Unknown

Follow-up Visits (suggested: monthly, quarterly x 12 months; annually thereafter)

Safety data (every visit – collected for time since previous visit)

Data Field	**Response field**
Adverse events	
Adverse events (AEOSI, SAE, unexpected AE)	Yes No
Which adverse event	FVIII inhibitors FIX inhibitors Thromboembolic events Autoimmune disorders Malignancies Liver disease Sensory paresthesias Infusion/Hypersensitivity reaction Hepatitis B (new or reactivation) Hepatitis C (new or reactivation) Serious complications due to immunosuppression Other
Serious complications due to immunosuppression	Hypertension Diabetes Severe infection Osteoporetic fracture Cataracts Other (specify)
If adverse event = malignancy:	
Has DNA sequencing been performed?	Yes No
Date	DD/MM/YYYY

Was there evidence of integration of plasmid (AAV) DNA into genomic DNA?	Yes No
Additional details regarding plasmid integration	Open field
Adverse event term	Text
Start date	DD/MM/YYYY
Is this event ongoing?	Yes No
Stop date	DD/MM/YYYY
Was this event considered serious?	Yes No
Seriousness criteria (select all that apply)	Fatal/death (please also complete Mortality form) Life-threatening Inpatient or prolonged hospitalization Persistent or significant disability/incapacity Congenital abnormality/birth defect Important medical event that may have jeopardized the patient and required medical or surgical intervention to prevent one of the outcomes listed above
Outcome	Recovered/Resolved Recovered/Resolved with sequelae Not recovered/Not resolved Fatal Unknown
Inhibitors tested against FVIII/FIX	Yes No Unknown
Date of test	DD/MM/YYYY
Type of test	Bethesda Nijmegen-Bethesda Mixing study Unknown
Result	Positive Negative Indeterminate
Titre (BU/mL)	Open field
Liver function tests	Yes No Unknown
Date of test	DD/MM/YYYY
Type of test	ALT AST Total bilirubin Alpha-fetoprotein Other (specify)
Result	Open field
Units	*Units for each test*
Value out of normal range	Yes, please explain No
Reference range (minimum)	Open field
Reference range (maximum)	Open field

If elevated enzymes: are there alternative diagnoses? (select all that apply)	High alcohol intake Nonalcoholic fatty liver disease Extreme exercise/exertion Concurrent viral infection Acetaminophen Gilbert's syndrome Other, specify
Liver assessment since last follow-up?	Liver biopsy Ultrasound CT scan MRI Fibrosis stage assessment
Date (most recent)	DD/MM/YYYY
Results (most recent)	Normal Abnormal, please explain
Has DNA sequencing been performed?	Yes No Unknown
Date	DD/MM/YYYY
Was there evidence of integration of plasmid (AAV) DNA into genomic DNA?	Yes No
Additional details	Open field
Liver biopsy: Was METAVIR score (activity grade) obtained?	Yes No
METAVIR score (Activity grade)	A0: no activity A1: mild activity A2: moderate activity A3: severe activity
Was a METAVIR score (fibrosis stage) obtained?	Yes No
Was a METAVIR score (fibrosis stage) obtained?	F0: no fibrosis F1: portal fibrosis without septa F2: portal fibrosis with few septa F3: numerous septa without cirrhosis F4: Cirrhosis
Fibrosis stage Methodology	Radiologic Serologic
Radiologic methodology	Fibroscan Other, specify
Score	Open field (numerical, 0-75)
Serologic methodology	Fibrotest/Fibrosure Hepascore FibroSpect ELF Score Other (please specify)
Score	Open field (numerical, 0-50, 2 decimals)
Has patient been diagnosed with liver disease?	Liver failure Cirrhosis Liver fibrosis and/or progression of liver fibrosis
Date of diagnosis	MM/YYYY
AAV Neutralizing antibodies	

Test methodology	Transduction inhibition assay Total antibody Other, specify
Date of test	MM/YYYY
Result	Positive Negative N/A
Titre (if recorded)	Open field
Concomitant Medications / Co-morbidities	
Have you received immunosuppressive therapy since last follow-up?	Yes No Unknown
Was it vector-related immunosuppressive therapy?	Yes No Unknown
Drug name	Open field
Dose	Open field
Units	Mg Other
Start date	DD/MM/YYYY
Ongoing?	Yes No
End date	DD/MM/YYYY
Onset of any other new co-morbidities	Yes No
Which new co-morbidity?	Respiratory disease Hypertension Kidney disease Diabetes Osteoarthritis Osteoporosis Rheumatoid arthritis Obesity Anxiety Depression Other, specify
Date of onset	DD/MM/YYYY
Ongoing	Yes No
Date of resolution	DD/MM/YYYY
Description	Open field

Efficacy data (every visit – collected for time since previous visit)

Data Field	Response field
Bleeding events	Yes No Unknown
Date	DD/MM/YYYY
Reason	Traumatic Non-traumatic
Was the bleed treated with hemostatic treatment	Yes No
Bleed Location	Joint

	Muscle Mucosal Head – intracranial Head – extracranial Other
FVIII/FIX activity level test *ability to enter >1 test result	Yes No Unknown
Date of test	MM/YYYY
Factor level (IU/dL)	Open field
Type of assay	One-stage Chromogenic Unknown
Assay reagents	Dropdown by manufacturer/reagent Other, specify
Use of any hemostatic treatment (factor, emicizumab, other)	Yes No
Hemostatic treatment type	Clotting factor concentrate Standard half-life Extended half-life Hemostatic rebalancing agents, specify Bispecific antibodies Emicizumab Other, specify Other
Start date of treatment	MM/YYYY
Ongoing?	Yes No
End date of treatment	MM/YYYY
Treatment drug	Dropdown of all factor and other treatment
Dose	Open field
Units	IU mg
Frequency	3 times per week 2 times per week 1 time per week 1 time per month 2 times per month Other, specify
Hemostatic treatment type	Prophylaxis – Continuous Prophylaxis – Event-based, short term or intermittent Episodic (On demand) Immune Tolerance Induction Other, specify Unknown
Use of any anticoagulant medication	Yes No
Date of treatment	MM/YYYY
Treatment drug	List
Reason for treatment	High factor level Atrial fibrillation Cardiac non-atrial fibrillation Arterial thrombosis

	Venous thrombosis Other, specify
Any change in concomitant medications since last visit (prescription, over-the-counter (OTC), herbal medications, and supplements)?	Yes No Unknown
Medication	List of medications (incl. over the counter) Other, please specify Unknown
Indication	Open field
Dose	Open field
Route	Open field
Start date	DD/MM/YYYY
Ongoing?	Yes No
End date	DD/MM/YYYY Option for ongoing

Surgeries (every visit – collected for time since previous visit)

Data Field	Response field
Surgeries	Yes No Unknown
What was the surgery	Abdominal surgery Orthopedic surgery Dental procedure Central device Neurosurgery Other, specify Unknown
Date	MM/YYYY
Did the surgery require factor?	Yes No
Factor details	List of CFCs
Total dose (IU/kg)	Open field
Start date	DD/MM/YYYY
Stop date	DD/MM/YYYY
Bleeding complication	Yes No
Additional intervention	Required red cell transfusion Other, specify

Quality of life (annual)

Patient Reported Outcome (annual)

Data Field	Response field
EQ-5D-5L	N/A
PROBE	N/A
coreHEM MHO*	N/A

*when it becomes available

Mortality

Data Field	Response field
Date of death	MM/YYYY

Death related to gene therapy	Yes No Unknown
Primary cause of death	Intracranial hemorrhage Bleeding (excluding intracranial) Thromboembolic event Liver disease, specify Cancer Cardiac Infection (including pneumonia) HIV Other, specify
Type of cancer	Leukemia Lymphoma Liver Lung Prostate Colorectal Stomach Breast Other, specify

End of registry

Data Field	**Response field**
Date of registry withdrawal	DD/MM/YYYY
Specify the reason for withdrawal	Lost to follow-up Patient withdrew consent Patient withdrawn by principal investigator Other Death Other, specify