DISEASE REGISTRY REPORT

Compound(s): Not applicable

Prevalence assessment of unrecognized mucopolysaccharidosis I, II, IVA, and VI in juvenile idiopathic arthritis patients with low inflammatory markers

Registry number: Not applicable

Study number: ASY13969

Registry initiation date [date first patient in (FPI)]: 18 February 2016

Registry completion date [last patient completed/last patient out (LPO)]: 25 April 2017

Report date: 14-June-2018

This registry was performed in compliance with the guidelines for Good Epidemiology Practice. This report has been prepared based on the publication 'Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) – Guidelines for reporting observational studies – Ann Intern Med. 2007'.

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SYNOPSIS

Title of the registry:	Prevalence assessment of unrecognized mucopolysaccharidosis (MPS) I, II, IVA, and VI in Juvenile Idiopathic Arthritis (JIA) patients with low inflammatory markers (ASY13969).
Design:	This was an international, multicenter, noninterventional study to evaluate the frequency of unrecognized MPS I, II, IVA, and VI in children with JIA, with low inflammatory markers (erythrocyte sedimentation rate [ESR] ≤20 mm/Hr and/or C Reactive Protein [CRP] ≤10 mg/L) using enzyme assay markers in a dried blood spot (DBS) assay. Overall, 500 patients were identified prospectively through screening of new and current patients presenting in experienced (tertiary care) pediatric rheumatology practices. The study duration for each patient was 1 single visit, which could have been conducted within several days. Patients who satisfied the inclusion/exclusion criteria and their parent(s)/legal guardian(s) provided informed consent/assent, underwent DBS blood sampling to screen for MPS I, II, IVA and VI, and were assessed for presence and duration of morning stiffness and pattern of joint involvement using Juvenile Arthritis Disease Activity (JADAS-27) score (Appendix 3.1 Protocol). Although the protocol referred to a registry, this study was confirmed not to be part of a registry.
Objectives:	Primary objective: To determine the prevalence of unrecognized MPS I (Hurler, Hurler-Scheie, or Scheie syndromes), II (Hunter syndrome), IVA (Morquio syndrome), and VI (Maroteaux-Lamy syndrome) patients among a population of pediatric rheumatology patients with low inflammatory markers (ESR and or CRP) using the DBS testing to screen for MPS. Secondary objective: To study the pattern of joint involvement in JIA patients.
Participants as of 25 April 2017:	It was planned for approximately 500 patients to be enrolled at 8 sites in 6 European countries. Inclusion criteria: • Male or female JIA patients, between 6 months and 18 years of age, inclusive. • History of JIA documented at an experienced pediatric rheumatology clinic. All JIA subtypes were included if the patient had at least 1 low ESR (≤20 mm/Hr) and/or CRP (≤10 mg/L) value measured at a preceding visit (timelines of the precedent visit were defined as per the patient standard of care) or at the study visit, and were assessed as being independent from concomitant anti-inflammatory/anti-infective treatments at the discretion of the Investigator. • Signed informed consent/assent obtained from patient and patient's legal representative (parents or guardians) according to local regulations (Appendix 3.4 Patient informed consent). Exclusion criteria: • Patients for whom MPS enzyme activity tests (ie, enzyme levels tested in fibroblasts, leukocytes, serum, or blood spots) had already been performed and for which the result was normal. (Patients who have been screened for MPS through urinary glycosaminoglycan (GAG) and tested normal may have been included in the study). • Patients with at least 1 high ESR (>20 mm/Hr) and/or CRP (>10 mg/L) value measured at a preceding visit or at the study visit, not related to an identified concomitant infection or intercurrent illness at the discretion of the Investigator. • Patient has any medical condition or extenuating circumstance which, in the opinion of the Investigator, could interfere with the patient's ability to complete the study procedure, or with the interpretation of study results.

Scientific committee and members:	Not applicable.
Medical study global coordinator:	[redacted] Rheumatology, Department of Pediatrics University Medical Center Utrecht. Lundlaan 6, 3584 EA Utrecht, PO Box 85090, The Netherlands
Publications (reference):	Not applicable.
Introduction - Background/ rationale:	Background: Mucopolysaccharidosis disorders are severe and potentially life-threatening genetic conditions that can cause extensive damage to multiple organ systems. Patients with MPS disorders lack the enzymes necessary to metabolize GAGs. Glycosaminoglycans then accumulate in multiple organ systems, leading to symptoms such as skeletal dysplasia, joint stiffness, hepatosplenomegaly, hernias, cardiac valvulopathy, spinal cord compression, communicating hydrocephalus, narrowed airways, frequent respiratory infections, sleep apnea, and coarse facies. There are 7 MPS disorders in total: MPS I, II, III, IV, VI, VII, and IX. While children with prominent manifestations are usually diagnosed early in life, patients with less prominent manifestations often go undiagnosed for years or decades. By this point, irreparable damage has often occurred. Prompt recognition is the key to early initiation of therapy, which is closely linked to the prognosis and outcome. Musculoskeletal stiffness and radiologic abnormalities are often the first manifestations of the MPS disorders that bring children who lack prominent manifestations to medical attention. However, these symptoms are often insufficient to prompt appropriate testing and diagnosis for MPS disorders. Because of the overlap of symptoms, MPS disorders can be misdiagnosed as JIA. However, MPS patients do not typically have the morning stiffness, joint swelling, laboratory indicators of inflammation (such as an elevated ESR), or erosive bone lesions seen in JIA (1). Rationale: There have been no previous prospective studies of the frequency at which children with unrecognized MPS disorders are seen in pediatric rheumatology clinics. The goal of this investigation was to determine how often children with unrecognized MPS I, II, IVA, and VI are presenting in experienced (tertiary care) pediatric rheumatology practices. Appropriate screening to determine the true prevalence of such presentation is an important first step in developing an educational program for physicians in such clinics to facilitate the recognition and appropriate referral of patients with MPS disorders. The DBS assay for MPS requires only a minimal amount of blood (less than 1 mL). This increases the feasibility of screening in infants, where larger blood samples may not be convenient or possible to obtain. In addition, DBS samples are taken on filter paper so they can be easily shipped in a regular envelope, and lysosomal enzymes are highly stable on the filter paper so they can be shipped by ground mail. Thus, DBS may help facilitate screening in multicenter studies, particularly over a large geographic area (2,3).
Methodology:	(a) Site and patient selection Overall, 501 patients were identified prospectively through screening of new and current patients, at 8 selected EU clinics experienced in pediatric rheumatology arthritis. Addition of sites could have occurred if there were recruitment issues. A second cohort of 500 patients would have been considered, and a possible extension of the study discussed, if no new MPS cases in the first 500 patients were identified; however, this did not occur during this study.

(b) Data collection

Data were collected using a single electronic case report form (eCRF) for each eligible patient (Appendix 3.3 Case report form).

(c) Safety data collection

Serious adverse event (SAEs) related to study procedure (blood collection) only that occurred during the course of the study must have been recorded and transmitted to the Sponsor within 24 hours. The physician was to take all appropriate measures to ensure the safety of the patients, notably he/she should follow up the outcome (clinical signs, laboratory values or other, etc.) of adverse-event (AE) related to blood drawing procedure until the return to normal or consolidation of the patient's condition. In case of any SAE related to blood drawing procedure, the patient was to be followed up until clinical recovery was complete and laboratory results returned to normal or until progression had been stabilized.

(d) Data management, review, evaluation:

Data quality control was performed at site level and remotely, in all of the active sites enrolled in each country. If specific issues were identified in some sites or countries, the percentage of quality control in the concerned site/country or in all sites/countries must have been appropriately increased and corrective actions set up. Quality control was performed by qualified designated personnel in each country. The physician must have kept all pertinent source documents (medical records, laboratory reports, etc.) for each patient and have agreed that the Company designee would have the direct and full access to the source documents for quality control.

(e) Statistical considerations:

As an observational study, no formal statistical hypothesis testing was planned with adequate power or the Type I error control. More details regarding statistical strategies could be found in the SAP (Appendix 3.2.1 Statistical analysis plan).

Analysis populations

Screened population

The screened population included all patients with a signed informed consent form (by the patient or parent).

Eligible population

The eligible population included all screened patients in the study, with a date of consent, meeting all inclusion criteria and no exclusion criteria.

Analysis population

The analysis population of patients included all eligible patients, for whom at least 1 DBS test had been performed.

Variables and evaluation criteria:

Patient characteristics data:

- Demographic variables including, gender, age, height, weight, body mass index (BMI; kg/m^2), and BMI by class
- Medical history including JIA history (time between initial JIA diagnosis and inclusion [years], and JIA category) and relevant medical/surgical history terms, if any
- Previous and concomitant medication (since 6 months prior to inclusion)
- Laboratory results including ESR (mm/hour) and CRP (mg/L)
- Mucopolysaccharidosis history and testing including previous biochemical testing for MPS disorders, symptoms suggestive of MPS disorders, and type of symptoms suggestive of MPS disorders.

	Descriptive analysis of all variables was provided on the analysis population overall and per study site and country. A listing of previous and ongoing medical/ surgical history was provided. All severe adverse events occurring during the blood sample collection were listed. Medical/ surgical history and SAEs related to study procedures were coded using Medical Dictionary for Regulatory Activities (MedDRA; version 20.0) and presented by number and percentage of patients, and per system organ class and preferred term in frequency tables. The quantitative variables were summarized using the number of available data, mean, standard deviation (SD), median, minimum, Q1, Q3, and maximum. The qualitative variables were summarized using the number of non-missing data, counts, and percentages. Percentages were calculated not accounting for missing values or unknown responses. Main evaluation variables: The main evaluation criterion was the percentage of patients with a positive screening result for MPS, I or II, or IVA, or VI based on DBS tests. Positive screening results were determined by the following thresholds: • Positive to MPS I if Alpha-L-iduronidase <100 pmol/spot*20h • Positive to MPS II if Iduronate-2-sulfatase (male only) <100 nmol/spot*20h • Positive to MPS IVA if N-acetylgalactosamine-6-sulfatase <0.69 pmol/punch*20h • Positive to MPS VI if Arylsulfatase B <0.08 nmol/spot*21h The number and percentage of positive, negative, and ambiguous patients per type of MPS were also calculated based on predetermined thresholds presented in Appendix 3.2.1 Statistical analysis plan. All main evaluation variables were presented on the analysis population overall and per study site and country. The number and percentage of patients screened positive to MPS I, II, IVA or VI overall and per type were described for the analysis population. The two-sided 95% Clopper-Pearson confidence interval (95% CI; PROC FREQ) was also presented. Quantitative results obtained with each enzyme were presented. Listings of MPS screening results were provided. Secondary evaluation variables: • Duration of morning stiffness (min) assessed the day of examination and proportion of patients with a reported duration (0 to 24 hours) • Evaluation of the severity of the pain due to illness (visual analogue scales [VAS] from 0 to 10 cm with 0 = no pain and 10 = very severe pain) • Active joint count (AJC) overall and stratified by side (left/right) and body part (upper extremities/lower extremities) including number of swollen joints (from 0 to 34), tender joints (from 0 to 41), and joints with a limitation of motion (from 0 to 37) • JADAS-27 score (from 0 to 57) defined as the sum of AJC (from 0 to 27), Patient Global Evaluation score (PGE; from 0 to 10), Physician Global Assessment score (PGA; from 0 to 10), and normalized ESR In case of missing PGE, PGA, or normalized ESR, the JADAS-27 score was considered as missing. Joints that were considered “not evaluable” were counted as having no limitation on motion for JADAS-27 score. A listing of JADAS-27 scores was provided. Secondary evaluation variables were displayed using descriptive statistics on the analysis population overall, per study site and per country. The results were displayed for patients identified as MPS patients (DBS screened positive patients) and JIA patients (patients not identified as DBS screened positive for any of the 4 MPS types and who were not identified as having a pre-analytical problem as described in Appendix 3.2.1 Statistical analysis plan [4.1.2]).

	Duration of stiffness (min) was quantitatively and qualitatively analyzed. Visual analogue scores associated to the evaluation of pain were quantitatively analyzed. In addition, mean number of swollen joints, tender joints or joints with limitation of motion were presented per joints and left/right side. The JADAS-27 score was described as a quantitative variable. Variables used to calculate this score were also displayed. Each variable was considered individually. Missing data were not imputed, instead number of patients with missing data were presented. For imprecise/ incomplete dates prior to the visit date, when the month was missing it was replaced by July and when the day was missing it was replaced by 15 for duration and time from calculations. If the imputed data was incoherent with the date of visit, then the imputation rule was modified accordingly. Sample size: An 83% power was calculated to detect at least 1 patient with MPS for a sample size of 500 patients, assuming a 0.35% true incidence rate. It was planned to recruit 500 patients in order to have 500 DBS samples analyzed and evaluable, across 8 European centers in 6 countries.
Registry period:	This report includes pediatric rheumatic disease data including data up to 25 April 2017. Although the protocol referred to a registry, this study was confirmed not to be part of a registry.
RESULTS Participants (actual):	(a) Overall participation status: The study screened 501 patients at 8 centers in 6 countries: Netherlands (1 center), Germany (1 center), Italy (2 centers), Slovenia (1 center), Spain (1 center), and Turkey (2 centers) (Appendix 2.1 Disposition of patients [Table 1.1]). The number of participating physicians was 34 (Appendix 1.8, Participating physicians). (b) Participation per period of the study: Five hundred and one patients with JIA were screened, and 501 patients met the study eligibility criteria (see Table 1; Appendix 2.1 Disposition of patients [Table 1.1]). Of the eligible population, 478 of 501 patients had at least 1 DBS test and no more than 1 MPS screening result classified as having a pre-analytical problem, and these patients were included in the analysis population. Across all sites, 23 of 501 patients were not included in the analysis population, including 8 patients who did not have a DBS test and 15 patients with a pre-analytical problem ([Table 1.1] and [Listing 1.1]).

Table 1 Disposition of patients – All patients (N=501)

		Germany N=54	Italy N=93	The Netherlands N=142	Slovenia N=60	Spain N=116	Turkey N=36	Total N=501
Screened population [1]	N	54	93	142	60	116	36	501
Eligible population [2]	N	54	93	142	60	116	36	501
	Yes	54 (100.0%)	93 (100.0%)	142 (100.0%)	60 (100.0%)	116 (100.0%)	36 (100.0%)	501 (100.0%)
Analysis population [3]	N	54	93	142	60	116	36	501
	No	1 (1.9%)	5 (5.4%)	1 (0.7%)	0 (0.0%)	15 (12.9%)	1 (2.8%)	23 (4.6%)
	Yes	53 (98.1%)	88 (94.6%)	141 (99.3%)	60 (100.0%)	101 (87.1%)	35 (97.2%)	478 (95.4%)
Exclusion from analysis population reason	N	1	5	1	0	15	1	23
	No DBS test performed	0 (0.0%)	1 (20.0%)	0 (0.0%)	0 (0.0%)	6 (40.0%)	1 (100.0%)	8 (34.8%)
	Pre-analytical problem	1 (100.0%)	4 (80.0%)	1 (100.0%)	0 (0.0%)	9 (60.0%)	0 (0.0%)	15 (65.2%)

[1] The screened population will include all patients with a signed Informed Consent Form (by the patient or the parent)
[2] The eligible population will include all screened patients in the study, with a date of consent, meeting all inclusion criteria and not meeting any of the exclusion criteria
[3]The analysis population of patients will include all eligible patients, for whom at least one DBS test has been performed and with no more than 1 MPS result classified as pre-analytical problem (such classification is defined in SAP section 4.1.2, final version 1.0 dated 09NOV2017).
Source: Appendix 2.1 Disposition of patients [Table 1.1].

Participant characteristics and primary analyses:

(a) Patient demographics and disease history:
Baseline demographic and disease history data are summarized by country and by site in Appendix 2.2 Patient's characteristics [2].

For the total analysis population, there was a greater number of female patients (335 [70.1%]) than male patients (143 [29.9%]) participating in the study; similar proportions of female to male patients were observed in each participating country, except Turkey, where at each of the 2 centers the proportion of female to male patients was approximately equal (Appendix 2.2.1 Demographic characteristics [Table 2.1.1] and [Table 2.1.2]).

The mean age (SD) for the total analysis population was 10.92 (4.23) years, with similar mean ages observed across the participating countries. The majority of patients in the total analysis population were >5 years of age, with 11.9% of patients being <5 years of age; 48.1% and 40.0% of patients being >5 to 12 years of age; and >12 to 18 years of age inclusive, respectively. Similar proportions of patients based on these age classes were observed across the participating countries (Appendix 2.2.1 Demographic characteristics [Table 2.1.1]). The mean BMI (SD) for the total analysis population was 18.70 (3.49) kg/m^2, with mean BMI values similar across the participating countries. The majority of patients were of a healthy weight (BMI class), with >77% of patients of a healthy weight in each participating country; 14.3% of the total analysis population were within the obesity BMI class; and 2.7% within the underweight category. Similar demographics results were observed for each site ([Table 2.1.2]).

The study was to include patients with any JIA subtype, with at least 1 low ESR (≤20 mm/Hr) and/or CRP (≤10 mg/L) value measured at a preceding visit or at the study visit. Overall for the analysis population by

	country or site, the most frequent JIA category (Appendix 2.2.2 Medical history [Table 2.2.1] and [Table 2.2.2]) was oligoarthritis (263 [55.0%] patients), followed by polyarthritis (rheumatoid factor negative; 101 [21.1%] patients), enthesitis related arthritis (39 [8.2%] patients), systemic arthritis (26 [5.4%] patients), psoriatic arthritis (25 [5.2%] patients), polyarthritis (rheumatoid factor positive; 14 [2.9%] patients), undifferentiated arthritis (7 [1.5%] patients), and unknown JIA category (3 [0.6%] patients). In the total analysis population by country or site, 469 (99.4%) patients were classified in the ESR class of ≤20 mm/Hr, with a mean (SD) ESR value of 6.26 (4.78) mm/hour; and 466 (98.9%) patients were classified in the CRP class (≤10 mg/L), with a mean (SD) CRP value of 2.19 (4.08) mg/L. Of the total analysis population, 3 patients had ESR values >20 mm/hour and 5 patients had CRP values >10 mg/L and the inclusion of these patients was confirmed by the Investigators (Appendix 2.2.4 Laboratory results [Table 2.4.1] and [Table 2.4.2] and [Listing 2.4.1]). Only 1 patient had been previously tested for urinary GAG and their result had been found to be normal; and therefore, could be included in the study as per the inclusion/exclusion criteria. No patients had been tested for MPS enzyme activity (Appendix 2.2.5 MPS history and testing [Table 2.5.1] and [Table 2.5.2]). The mean (SD) number of years between initial JIA diagnosis and inclusion in the study for the total analysis population was 4.94 (3.47) years, with means generally similar across the participating countries and participating sites (Appendix 2.2.2 Medical history [Table 2.2.1] and [Table 2.2.2], respectively). Prior relevant medical/surgical history by country or site is summarized in Appendix 2.2.2 Medical history [Table 2.2.3] and [Table 2.2.4], respectively. In addition, concomitant relevant medical/surgical history by country or site is summarized in [Table 2.2.5] and [Table 2.2.6], respectively. Overall, the number of patients with reported prior or concomitant relevant medical/surgical history was low, with 40 (8.4%) and 86 (18.0%) patients, respectively (Appendix 2.2.2 Medical history [Table 2.2.3] and [Table 2.2.5], respectively). The most frequently reported prior or concomitant relevant medical/surgical history reported was uveitis, with 37 (7.7%) patients in the total analysis population reporting it as a concomitant medical history. Other concomitant relevant medical histories reported were coeliac disease (5 [1.0%] patients) attention deficit/hyperactivity disorder (4 [0.8%] patients), autoimmune thyroiditis (4 [0.8%] patients), mite allergy (3 [0.6%] patients), and rhinitis allergic (3 [0.6%] patients). All other concomitant relevant medical/surgical histories were reported by 2 or less patients. The majority of reported prior or concomitant uveitis cases were reported at the site in Spain, with 1 (1.0%) and 36 (35.6%) patients prior or concomitant uveitis, respectively ([Table 2.2.4] and [Table 2.2.6], respectively). Prior or concomitant medication within 6 months of inclusion by country or site is summarized in Appendix 2.2.3 Prior and concomitant medication [Table 2.3.1] and [Table 2.3.2], respectively. Overall, 361 (76.8%) patients received at least 1 concomitant medication within 6 months from inclusion. The most prevalent concomitant medication being taken by patients in the total analysis population was methotrexate (234 [49.0%] patients) followed by tumor necrosis factor (TNF) alpha inhibitors (132 [27.6%] patients), and non-steroidal anti-inflammatory drugs (NSAIDs; 75 [15.7%] patients), with other types reported in less than 10% of patients. Across all countries, Methotrexate was the most prevalent except for in Turkey, where NSAIDs were most prevalent. Overall, there were 108 (22.6%) patients who had at least 1 suspicious symptom suggestive of a MPS disorder (Appendix 2.2.5 MPS history and testing [Table 2.5.3] and [Table 2.5.4]). The number of subjects reported to have at least 1 suspicious symptom suggestive of MPS was highly variable across the countries and sites. One center in Italy (002) reported at least 1 suspicious symptom in 48 (100.0%) patients; one center in Turkey (002) reported 5 (100.0%) patients; the center in Slovenia reported 23 (38.3%) patients; the center in The Netherlands reported 29 (20.6%) patients; the other center in Turkey (001) reported 2 (6.7%) patients; the center in Germany reported 1 (1.9%) patient; and the other center in Italy (001) and the center in Spain reported no patients. The most prevalent suspicious symptom suggestive of MPS disorders was joint stiffness or limited range of motion (bones and joints; overall 99 [20.7%] patients), reported in 47 (97.9%) patients at 1 center in Italy (002), 25 (17.7%) patients at the center in The Netherlands, 22 (36.7%) patients at the center in Slovenia, and 5 (100.0%) patients at 1 center in Turkey (002). Other frequently reported suspicious

symptoms were hand problems (5 [1.0%] patients), frequent upper respiratory tract infections (5 [1.0%] patients), copious nasal discharge (4 [0.8%] patients), and short stature (4 [0.8%] patients). All other reported suspicious symptoms were in 3 or less patients.

(b) Primary objective:

Of the total analysis population, 38 (7.9%) patients had a positive MPS screening result and 440 (92.1%) patients did not have a positive MPS screening result (see Table 2; Appendix 2.3 Primary Objective [Table 3.1] and [Table 3.2]). All countries except Turkey had a patient with a positive MPS screening result, with the highest proportion of patients observed in Germany (10 [18.9%] patients), then Slovenia (9 [15.0%] patients), Italy (9 [10.2%] patients), The Netherlands (8 [5.7%] patients), and then Spain (2 [2.0%] patients). The proportion of patients with any positive MPS screening result was comparable between the 2 centers in Italy (10.0% and 10.4%, respectively).

Table 2 DBS result – By country – Analysis population (N=478)

		Germany N=53	Italy N=88	The Netherlands N=141	Slovenia N=60	Spain N=101	Turkey N=35	Total N=478
Any positive MPS result	N	53	88	141	60	101	35	478
	Missing values	0	0	0	0	0	0	0
	No	43 (81.1%) [68.6 ; 89.4]	79 (89.8%) [81.7 ; 94.5]	133 (94.3%) [89.2 ; 97.1]	51 (85.0%) [73.9 ; 91.9]	99 (98.0%) [93.1 ; 99.5]	35 (100.0%) [90.1 ; 100.0]	440 (92.1%) [89.3 ; 94.2]
	Yes	10 (18.9%) [10.6 ; 31.4]	9 (10.2%) [5.5 ; 18.3]	8 (5.7%) [2.9 ; 10.8]	9 (15.0%) [8.1 ; 26.1]	2 (2.0%) [0.5 ; 6.9]	0 (0.0%) [- ; -]	38 (7.9%) [5.8 ; 10.7]
Alpha-L-iduronidase (MPS I)	N	53	88	140	59	101	35	476
	Missing values	0	0	1	1	0	0	2
	Positive	0 (0.0%) [- ; -]	0 (0.0%) [- ; -]	6 (4.3%) [2.0 ; 9.0]	0 (0.0%) [- ; -]	0 (0.0%) [- ; -]	0 (0.0%) [- ; -]	6 (1.3%) [0.6 ; 2.7]
	Ambiguous	0 (0.0%) [- ; -]	0 (0.0%) [- ; -]	0 (0.0%) [- ; -]	0 (0.0%) [- ; -]	1 (1.0%) [0.2 ; 5.4]	0 (0.0%) [- ; -]	1 (0.2%) [0.0 ; 1.2]
	Negative	53 (100.0%) [93.2 ; 100.0]	88 (100.0%) [95.8 ; 100.0]	134 (95.7%) [91.0 ; 98.0]	59 (100.0%) [93.9 ; 100.0]	100 (99.0%) [94.6 ; 99.8]	35 (100.0%) [90.1 ; 100.0]	469 (98.5%) [97.0 ; 99.3]
Iduronate-2-sulfatase (MPS II) (males only)	N	16	23	50	14	25	15	143
	Missing values	0	0	0	0	0	0	0
	Positive	0 (0.0%) [- ; -]	0 (0.0%) [- ; -]	0 (0.0%) [- ; -]	0 (0.0%) [- ; -]	0 (0.0%) [- ; -]	0 (0.0%) [- ; -]	0 (0.0%) [- ; -]
	Ambiguous	0 (0.0%) [- ; -]	1 (4.3%) [0.8 ; 21.0]	0 (0.0%) [- ; -]	0 (0.0%) [- ; -]	1 (4.0%) [0.7 ; 19.5]	0 (0.0%) [- ; -]	2 (1.4%) [0.4 ; 5.0]
	Negative	16 (100.0%) [80.6 ; 100.0]	22 (95.7%) [79.0 ; 99.2]	50 (100.0%) [92.9 ; 100.0]	14 (100.0%) [78.5 ; 100.0]	24 (96.0%) [80.5 ; 99.3]	15 (100.0%) [79.6 ; 100.0]	141 (98.6%) [95.0 ; 99.6]

			Germany N=53	Italy N=88	The Netherlands N=141	Slovenia N=60	Spain N=101	Turkey N=35	Total N=478
N-acetylgalactosamine-6-sulfatase (MPS IVa)	N		50	81	134	55	95	24	439
	Missing values		3	7	7	5	6	11	39
	Positive		8 (16.0%) [8.3 ; 28.5]	1 (1.2%) [0.2 ; 6.7]	2 (1.5%) [0.4 ; 5.3]	1 (1.8%) [0.3 ; 9.6]	0 (0.0%) [- ; -]	0 (0.0%) [- ; -]	12 (2.7%) [1.6 ; 4.7]
	Ambiguous		0 (0.0%) [- ; -]	0 (0.0%) [- ; -]	0 (0.0%) [- ; -]	0 (0.0%) [- ; -]	0 (0.0%) [- ; -]	0 (0.0%) [- ; -]	0 (0.0%) [- ; -]
	Negative		42 (84.0%) [71.5 ; 91.7]	80 (98.8%) [93.3 ; 99.8]	132 (98.5%) [94.7 ; 99.6]	54 (98.2%) [90.4 ; 99.7]	95 (100.0%) [96.1 ; 100.0]	24 (100.0%) [86.2 ; 100.0]	427 (97.3%) [95.3 ; 98.4]
Arylsulfatase B (MPS VI)	N		53	88	140	59	101	35	476
	Missing values		0	0	1	1	0	0	2
	Positive		2 (3.8%) [1.0 ; 12.8]	8 (9.1%) [4.7 ; 16.9]	0 (0.0%) [- ; -]	8 (13.6%) [7.0 ; 24.5]	2 (2.0%) [0.5 ; 6.9]	0 (0.0%) [- ; -]	20 (4.2%) [2.7 ; 6.4]
	Ambiguous		2 (3.8%) [1.0 ; 12.8]	5 (5.7%) [2.5 ; 12.6]	12 (8.6%) [5.0 ; 14.4]	6 (10.2%) [4.7 ; 20.5]	18 (17.8%) [11.6 ; 26.4]	5 (14.3%) [6.3 ; 29.4]	48 (10.1%) [7.7 ; 13.1]
	Negative		49 (92.5%) [82.1 ; 97.0]	75 (85.2%) [76.3 ; 91.2]	128 (91.4%) [85.6 ; 95.0]	45 (76.3%) [64.0 ; 85.3]	81 (80.2%) [71.4 ; 86.8]	30 (85.7%) [70.6 ; 93.7]	408 (85.7%) [82.3 ; 88.6]

The two-sided 95% Confidence Interval is computed according to Clopper-Pearson method
Source: Appendix 2.3 Primary objective [Table 3.1]

Of the total analysis population, 6 (1.3%) patients were positive for MPS I screening, no patients were positive for MPS II screening, 12 patients (2.7%) were positive for MPS IVA screening, and 20 patients (4.2%) were positive for MPS VI screening. The positive MPS screening results were variable across the countries and sites, with all 6 patients positive for MPS I screening at the site in The Netherlands; the majority of patients positive for MPS IVA screening (8 of 12) were at the site in Germany, with only 2 patients at The Netherlands site,1 patient at a site in Italy, and 1 patient at a site in Slovenia; and for MPS VI screening, 8 of 20 patients were across the sites in Italy, 8 patients were at the site in Slovenia, 2 patients were at the site in Spain, and 2 patients were at the site in Germany.

Quantitative DBS results for MPS across the countries and sites are summarized in Appendix 2.3 Primary Objective [Table 3.3] and [Table 3.4], respectively. In general, mean levels across countries and sites were similar for all 4 MPS' analyzed. Individual MPS values for each subject are presented in [Listing 3.1].

Other analyses:

Secondary objectives:

(a) Duration of morning stiffness

Of the 478 patients, 5 patients were missing morning stiffness data. Of the 473 patients, 393 (83.1%) patients had no morning stiffness (0 minutes), 56 (11.8%) patients had morning stiffness lasting

between 15 and 60 minutes (inclusive), 17 (3.6%) patients had morning stiffness lasting <15 minutes, 5 (1.1%) patients had morning stiffness >60 minutes and ≤120 minutes, and 2 (0.4%) patients had morning stiffness lasting >120 minutes. The mean (SD) duration of morning stiffness was 5.86 (19.55) minutes for the total analysis population. The mean duration was similar across countries and sites, with the exception of Germany, where the mean (SD) duration of morning stiffness was 1.89 (9.16) minutes (Appendix 2.4.1 Duration of morning stiffness [Table 4.1.1] and [Table 4.1.2], respectively). The mean (SD) duration of morning stiffness for just those with morning stiffness was 34.64 (35.70) minutes.

Analysis of morning stiffness by MPS screening status (Table 3) demonstrated that there were 34 of 38 patients (89.5%) positive for MPS screening that did not have morning stiffness; 2 (5.3%) patients did have morning stiffness, which lasted <15 minutes and 2 (5.3%) patients had morning stiffness which lasted between 15 and 60 minutes (inclusive). For patients with no positive MPS screening result (JIA patients), 359 of 435 patients (82.5%) did not have any morning stiffness, 76 patients did have morning stiffness, and 5 patients had missing data for this parameter. The mean (SD) duration of morning stiffness for those with a positive MPS screening result was 2.26 (10.04) minutes compared to 6.17 (20.15) minutes for patients with no positive MPS screening result (JIA patients). The mean (SD) duration of morning stiffness for only those with morning stiffness was 21.50 (26.31) minutes for patients with a positive MPS screening result compared to 35.33 (36.12) minutes for patients with no positive MPS screening result (JIA patients) (Appendix 2.4.1 Duration of morning stiffness [Table 4.1.3]).

Table 3: Duration of morning stiffness – by DBS test profile – Analysis population (N=478)

		MPS patients N=38	JIA patients N=440	Total N=478
Duration of morning stiffness (min)	N	38	435	473
	Missing values	0	5	5
	Mean ± SD	2.26 ± 10.04	6.17 ± 20.15	5.86 ± 19.55
	Median	0.00	0.00	0.00
	Q1 ; Q3	0.00 ; 0.00	0.00 ; 0.00	0.00 ; 0.00
	Min ; Max	0.0 ; 60.0	0.0 ; 180.0	0.0 ; 180.0
Duration of morning stiffness (class)	N	38	435	473
	Missing values	0	5	5
	Absent	34 (89.5%)	359 (82.5%)	393 (83.1%)
	< 15 min	2 (5.3%)	15 (3.4%)	17 (3.6%)
	≥ 15 and ≤ 60 min	2 (5.3%)	54 (12.4%)	56 (11.8%)
	> 60 min and ≤ 120 min	0 (0.0%)	5 (1.1%)	5 (1.1%)
	> 120 min	0 (0.0%)	2 (0.5%)	2 (0.4%)
Duration of morning stiffness for values > 0 (min)	N	4	76	80
	Missing values	0	5	5
	Mean ± SD	21.50 ± 26.31	35.33 ± 36.12	34.64 ± 35.70
	Median	12.50	30.00	25.00
	Q1 ; Q3	5.50 ; 37.50	15.00 ; 30.00	15.00 ; 30.00
	Min ; Max	1.0 ; 60.0	5.0 ; 180.0	1.0 ; 180.0

Source: Appendix 2.4.1 Duration of morning stiffness [Table 4.1.3]

(b) Active joint count

The majority of patients in the total analysis population did not have any swollen joints (387 [81.0%] patients), tender joints (362 [75.7%] patients), or joints with limited motion (362 [75.7%] patients) at the time of the study. The mean number of patients with no active joint count was similar across the countries and sites (Appendix 2.4.2 Active joint count [Table 4.2.1] and [Table 4.2.2], respectively); except for Turkey whereby 1 center had more patients with active joint counts (site 792-001 joint count >0: 70.0% patients had swollen joints, 86.7% patients had tender joints, and 83.3% patients had joints with limited motion) than none.

Analysis of the joint count by MPS screening status (Table 4) demonstrated that similar proportions of MPS screening positive or JIA patients (patients with no positive screening MPS result) were observed to have a joint count of 0; with 31 (81.6%) and 356 (80.9%) patients, respectively, having no swollen joints; 29 (76.3%) and 333 (75.7%) patients, respectively, having no tender joints; and 30 (78.9%) and 332 (75.5%) patients having no joints with limited motion (Appendix 2.4.2 Active joint count [Table 4.2.3]). However, patients with no positive MPS screening results (JIA patients) tended to have a higher number of swollen joints, tender joints, and joints with limited motion than MPS screening positive patients; with 9.8% of JIA patients having 2 or more swollen joints compared to 5.2% of MPS screening positive patients; with 13.8% of JIA patients having 2 or more tender joints compared to 7.9% MPS screening positive patients; and 13.4% of JIA patients having 2 or more joints with limited motion compared to 5.2% in MPS screening positive patients.

Table 4 Active Joint count – Overview of joint count by DBS test profile – Analysis population (N=478)

		MPS patients N=38	JIA patients N=440	Total N=478
Number of swollen joints	N	38	440	478
	Missing values	0	0	0
	0	31 (81.6%)	356 (80.9%)	387 (81.0%)
	1	5 (13.2%)	41 (9.3%)	46 (9.6%)
	2	1 (2.6%)	18 (4.1%)	19 (4.0%)
	3	0 (0.0%)	5 (1.1%)	5 (1.0%)
	4	0 (0.0%)	4 (0.9%)	4 (0.8%)
	5	0 (0.0%)	2 (0.5%)	2 (0.4%)
	6	0 (0.0%)	6 (1.4%)	6 (1.3%)
	7	1 (2.6%)	1 (0.2%)	2 (0.4%)
	8	0 (0.0%)	1 (0.2%)	1 (0.2%)
	9	0 (0.0%)	3 (0.7%)	3 (0.6%)
	10	0 (0.0%)	2 (0.5%)	2 (0.4%)
	16	0 (0.0%)	1 (0.2%)	1 (0.2%)

Source: Appendix 2.4.2 Active joint count [Table 4.2.3]

Table 4. continued

		MPS patients N=38	JIA patients N=440	Total N=478
Number of tender joints	N	38	440	478
	Missing values	0	0	0
	0	29 (76.3%)	333 (75.7%)	362 (75.7%)
	1	6 (15.8%)	46 (10.5%)	52 (10.9%)
	2	0 (0.0%)	29 (6.6%)	29 (6.1%)
	3	0 (0.0%)	6 (1.4%)	6 (1.3%)
	4	0 (0.0%)	10 (2.3%)	10 (2.1%)
	5	0 (0.0%)	6 (1.4%)	6 (1.3%)
	6	0 (0.0%)	2 (0.5%)	2 (0.4%)
	7	2 (5.3%)	1 (0.2%)	3 (0.6%)
	8	0 (0.0%)	2 (0.5%)	2 (0.4%)
	9	0 (0.0%)	1 (0.2%)	1 (0.2%)
	10	0 (0.0%)	2 (0.5%)	2 (0.4%)
	11	1 (2.6%)	0 (0.0%)	1 (0.2%)
	15	0 (0.0%)	1 (0.2%)	1 (0.2%)
	36	0 (0.0%)	1 (0.2%)	1 (0.2%)

Source: Appendix 2.4.2 Active joint count [Table 4.2.3]

Table 4. continued

		MPS patients N=38	JIA patients N=440	Total N=478
Number of joints with a limitation of motion	N	38	440	478
	Missing values	0	0	0
	0	30 (78.9%)	332 (75.5%)	362 (75.7%)
	1	6 (15.8%)	49 (11.1%)	55 (11.5%)
	2	1 (2.6%)	22 (5.0%)	23 (4.8%)
	3	0 (0.0%)	11 (2.5%)	11 (2.3%)
	4	1 (2.6%)	10 (2.3%)	11 (2.3%)
	5	0 (0.0%)	3 (0.7%)	3 (0.6%)
	6	0 (0.0%)	4 (0.9%)	4 (0.8%)
	7	0 (0.0%)	1 (0.2%)	1 (0.2%)
	8	0 (0.0%)	1 (0.2%)	1 (0.2%)
	9	0 (0.0%)	1 (0.2%)	1 (0.2%)
	10	0 (0.0%)	3 (0.7%)	3 (0.6%)
	11	0 (0.0%)	1 (0.2%)	1 (0.2%)
	17	0 (0.0%)	2 (0.5%)	2 (0.4%)

Source: Appendix 2.4.2 Active joint count [Table 4.2.3]

The proportion of MPS screening positive patients compared to MPS screening negative patients with no active joint count was generally similar between side (left/right) and body part (lower/upper extremities) (Appendix 2.4.2 Active joint count [Table 4.2.6]). In addition, frequency tables of active joint count for side (left/right) and body part (lower/upper extremities) are presented by country and site in [Table 4.2.4] and [Table 4.2.5], respectively. Frequency tables of active joint count by joint are presented for overall population ([Table 4.2.7]), by each individual country ([Table 4.2.8] to [Table 4.2.13]), by individual site

	([Table 4.2.14] to [Table 4.2.21]), and by DBS test profile for MPS patients and JIA patients ([Table 4.2.22] to [Table 4.2.23]), respectively. (c) Severity of pain and JADAS-27 The severity of pain and JADAS-27 scores across each country or site were variable. The sites in Turkey, which had no patients with a positive MPS screening result (JIA patients), had the highest means at both sites, for each pain or assessment score compared to the other countries or sites (Appendix 2.4.3 Severity of pain and JADAS-27 [Table 4.3.1] and [Table 4.3.2]). Mean patient pain evaluation was slightly lower in MPS screening positive patients compared to JIA patients, with mean (SD) values of 0.7 (1.2) cm and 1.1 (1.9) cm, respectively. The AJC-27 score was identical for MPS screening positive and JIA patients (0.8 [2.1] and 0.8 [2.2], respectively). Mean PGE was slightly lower in MPS screening positive patients compared to JIA patients, with mean (SD) values of 0.6 (1.1) cm and 1.1 (1.9) cm, respectively. The PGA score was identical for MPS screening positive and JIA patients (0.8 [1.9] and 0.8 [1.4], respectively). Mean JADAS-27 score was slightly lower in MPS screening positive patients compared to JIA patients, with mean (SD) values of 2.2 (4.3) cm and 2.7 (4.6) cm, respectively. The majority of patients had a JADAS-27 score of $\leq$1 (64.9% versus 58.1%). The proportion of patients in each JADAS-27 score class >1 was generally similar between MPS screening positive and JIA patients (Appendix 2.4.3 Severity of pain and JADAS-27 [Table 4.3.3]). JADAS-27 score for all patients are listed in [Listing 4.3.1]. Safety analysis: No adverse events were reported during the study.
Discussions:	(a) Key results Of the 501 JIA patients enrolled into this study, 38 patients (7.9%) screened positive for MPS and 440 patients did not screen positive for MPS (JIA patients) using a DBS test. These 38 patients were considered to be at a higher risk of having an MPS disorder. No patients were identified as screening positive for MPS II, and the proportions of patients screening positive for MPS I, IVA, or VI were generally similar. The occurrence of patients screening positive for MPS and the type of MPS were variable across the countries and sites, with the highest proportion of patients identified in Germany and very few or no patients identified in Spain and Turkey, respectively. At the time of the study visit, slightly lower proportions of patients who were screened MPS positive compared to those who had no positive MPS screening result (JIA patients) reported morning stiffness, with 4 of 38 MPS positive screened patients and 76 of 440 JIA patients. The mean duration of morning stiffness in patients positive for morning stiffness was lower in MPS positive screened patients compared to JIA patients, with mean (SD) durations of 21.50 (26.31) and 35.33 (36.12) minutes, respectively. The proportions of MPS positive screened patients or JIA patients who did not have an active joint count for swollen joints (81.6% versus 80.9%), tender joint (76.3% versus 75.7%), or joints with limited motion (78.9% versus 75.5%) were similar. However, JIA patients who had an active joint count tended to have a higher number of swollen joints, tender joints, or joints with limited motion compared to MPS positive screened patients. In addition, for some pain assessments and scores, slightly lower scores were observed in MPS screening positive patients compared to JIA patients. For instance, the mean patient pain evaluation values, mean PGE values, and mean JADAS-27 scores were slightly lower in MPS positive screened patients compared to JIA patients, but AJC-27 and PGA scores were identical between the sub-groups of patients. (b) Interpretation This study has a number of limitations that recommend caution in interpreting the results. Following identification of patients who have screened positive for MPS, further tests would be needed to confirm diagnosis, as false positive results can be inherent to screening tests, and therefore this should be taken into account when interpreting the results. In addition, the small sample size of MPS positive screened patients and a mixed population of MPS

	disorders limited the interpretation of the secondary objectives, such as joint count, joint pain, and morning stiffness in MPS patients. A further limitation of the study was that data for the secondary objective were only collected on a single visit. Data for these assessments over time may provide a more accurate profile of morning stiffness, active joint count, and/or pain in MPS positive screened and JIA patients. In addition, the primary analysis was performed on patients who already had symptoms and were considered to have JIA; further MPS positive screened patients may be identified by screening a wider population or other populations of children.
Conclusions:	This study performed at 8 sites over 6 countries identified 38 out of 478 children within pediatric rheumatology clinics, who screened positive for MPS and therefore, have a higher risk of having an MPS disorder. The proportions of patients screening positive for MPS I (6/476; 1.3%), IVA (12/439; 2.7%), or VI (20/476; 4.2%) were generally similar, with no patients identified for MPS II. However, further confirmatory testing would be needed to fully confirm an MPS disorder. Of those identified as MPS screening positive, it was observed that the incidence and duration of morning stiffness was slightly lower than that observed in patients with no positive DBS result (JIA patients). The proportion of MPS screening positive patients with joint involvement was similar to that of JIA patients; however, JIA patients with joint involvement appeared to have a higher number of joints involved compared to MPS screening positive patients. Slightly lower pain assessment values and scores were observed in MPS screening positive patients compared to JIA patients.
Date of report:	14-Jun-2018

APPENDICES

1 APPENDIX I – ADMINISTRATIVE AND LEGAL CONSIDERATIONS

1.1 ETHICAL CONSIDERATIONS

1.1.1 Ethical principles

This study was conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) including all subsequent amendments.

1.1.2 Laws and regulations

This study was conducted in accordance with the European guidelines for Good Epidemiology Practice (4), and in compliance with all international guidelines, and national laws and regulations of the country(ies) in which the study was performed, as well as any applicable guidelines.

Each participating country locally ensured that all necessary regulatory submissions (eg, IRB/IEC) were performed in accordance with local regulations including local data protection regulations.

For Regulatory authorities' submissions by country refer to Appendix 3.7 Regulatory authorities' submissions by country.

1.2 DATA PROTECTION

The patient's personal data and physician's personal data which were to be included in the Company's databases were treated in compliance with all local applicable laws and regulations.

When archiving or processing personal data pertaining to the physician and/or to the patients, the Company took all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

1.3 RECORD RETENTION

The physician was responsible for the retention of the study documentation until the end of the study. In addition, the physician had to comply with specific local regulations and recommendations regarding patient record retention.

1.4 THE COMPANY AUDITS AND INSPECTIONS BY COMPETENT AUTHORITIES (CA)

The physician agreed to allow the Company's auditors and Competent Authorities' inspectors to have direct access to records of the study for review, it being understood that all personnel with

access to patients' records are bound by professional secrecy and as such, could not disclose any personal identity or personal medical information.

The physician had to make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents. As soon as notification from the authorities for an inspection was received by the physician, he/she had to inform the Company and authorize the Company to participate in this inspection. The confidentiality of the data to verify the protection of the patients must be respected during these inspections. Any results or information arising from the inspections by the Competent Authorities were to be immediately communicated by the physician to the Company. The physician had to take appropriate measures required by the Company to ensure corrective actions for all problems found during audits and inspections.

1.5 CENTRAL LABORATORY

Blood samples collected during DBS testing were obtained using finger prick or venipuncture and placed on specialized filter paper. Samples were placed into patient-specific envelopes and sent for the determination of MPS I, II, IVA, and VI by analysis of enzyme activity to Dr. Z. Lukacs, Metabolic Laboratory, Hamburg University Medical Center, Department of Pediatrics and Institute of Clinical Chemistry - Building N23, House N23, Martinistr. 52, 20246, Hamburg, Germany.

1.6 OWNERSHIP OF DATA AND USE OF REGISTRY RESULTS

Unless otherwise specified by local laws and regulations, the Company retains ownership of data, results, reports, findings, and discoveries related to the study. Therefore, the Company reserves the right to use the data from the present study for any purpose, including to submit them to the Competent Authorities of any country.

1.7 REGISTRY CONSULTANTS

1.7.1 Scientific committee and charter

Not applicable.

1.7.2 Global coordination

Medical Study Coordinator:

[redacted]
Rheumatology, Department of Pediatrics
University Medical Center Utrecht. Lundlaan
6, 3584 EA Utrecht, PO Box 85090
The Netherlands

1.7.3 Other experts/consultants

Not applicable.

1.8 PARTICIPATING PHYSICIANS

The physicians performed the study in accordance with the protocol, applicable local regulations and international guidelines (Appendix 3.5.1, List of investigators who have enrolled).

The physician or a person designated by the physician, fully informed the patient, in language and terms they were able to understand, to the fullest extent possible, about the study, objectives, constraints, duration, and patient's rights.

It was the responsibility of the physician or a person designated by the physician to obtain written and signed informed consent from patients prior to inclusion. The patient's legal representative could also sign the written informed consent form (ICF) on behalf of the patient (Appendix 3.4 Patient informed consent). A copy of the signed and dated written ICF was provided to the patient and/ or his legal representative.

1.9 REGISTRY PERSONNEL

1.9.1 Personnel involved in the study

The Company responsible medical officer approved this report by eSignature (Appendix 3.8 Report approval).

This report was prepared by

- [redacted], Study Medical Manager
- [redacted], Study Medical Manager back-up
- [redacted], Statistician
- [redacted], Global Safety Manager
- [redacted], Global Safety Expert
- [redacted], Global Study Manager
- [redacted], Medical Writer
- [redacted], Medical Writer (Covance CRO)

1.9.2 The Company internal staff

The Company was responsible for providing adequate resources to ensure the proper conduct of the study.

The Company was responsible for local submission(s) complying with data protection rules and any other local submission(s) required.

1.9.3 Service provider

Medical Writing of the Clinical Study Report (CSR) was carried out by Covance Clinical Research Unit Ltd, Leeds, UK under the supervision of the Company.

International Clinical Trial Association (ICTA), 11 Rue du Bocage, Fontaine Les Dijon, 21121, France, developed the electronic Case Report Form (CRF) and performed data management activities, under the supervision of the Company.

2 APPENDIX II – TABLES AND GRAPHS

2.1 DISPOSITION OF PATIENTS

See Appendix 2.1 Disposition of patients [1]

2.2 PATIENT'S CHARACTERISTICS

2.2.1 Demographic characteristics

See Appendix 2.2.1 Demographic characteristics [2.1]

2.2.2 Medical history

See Appendix 2.2.2 Medical history [2.2]

2.2.3 Prior and concomitant medication

See Appendix 2.2.3 Prior and concomitant medication [2.3]

2.2.4 Laboratory results

See Appendix 2.2.4 Laboratory results [2.4]

2.2.5 MPS history and testing

See Appendix 2.2.5 MPS history and testing [2.5]

2.3 PRIMARY OBJECTIVE

See Appendix 2.3 Primary objective [3]

2.4 SECONDARY OBJECTIVE

2.4.1 Duration of morning stiffness

See Appendix 2.4.1 Duration of morning stiffness [4.1]

2.4.2 Active joint count

See Appendix 2.4.2 Active joint count [4.2]

2.4.3 Severity of pain and JADAS-27

See Appendix 2.4.3 Severity of pain and JADAS-27 [4.3]

2.5 SAFETY DATA

See Appendix 2.5 Safety data [5]

3 APPENDIX III – SUPPORTIVE DOCUMENTS

3.1 PROTOCOL

Appendix 3.1 Protocol - Version 1.0 - dated 24 June 2015

3.2 STATISTICAL ANALYSIS PLAN (SAP)

3.2.1 Final statistical analysis plan

Appendix 3.2.1 Statistical analysis plan - Version 1.0 - dated 09 November 2017

3.2.2 Changes from the final Statistical Analysis Plan

Not applicable.

3.3 CASE REPORT FORM (CRF)/ PATIENT QUESTIONNAIRE

Appendix 3.3 Case report form

3.4 PATIENT INFORMED CONSENT

Appendix 3.4 Patient informed consent form [from 5 to 11 years]

Appendix 3.4 Patient informed consent form [from 12 to 17 years]

Appendix 3.4 Patient informed consent form [Assent form for parent]

3.5 OTHER DOCUMENTS RELEVANT TO THE REGISTRY

3.5.1 List of investigators who have enrolled

Appendix 3.5.1 List of investigators who have enrolled

3.6 OTHER REGISTRY INFORMATION

Not applicable.

3.7 REGULATORY AUTHORITIES' SUBMISSIONS BY COUNTRY

Available upon request.

3.8 REPORT APPROVAL

3.8.1 Coordinating Physician's approval

Not applicable.

3.8.2 The Company's approval

The Company's responsible medical officer approved this report by eSignature.

4 APPENDIX IV - PUBLICATIONS

4.1 REFERENCES

1. Cimaz R, Coppa GV, Kone-Paut I, Link B, Pastores GM, Elorduy MR, et al. Joint contractures in the absence of inflammation may indicate mucopolysaccharidosis. Pediatr Rheumatol Online J. 2009;7:18.

2. Aldenhoven M, de Konig TJ, Verheijen FW, Prinsen BH, Wijburg FA, van der Ploeg FA, et al. Dried blood spot analysis: an easy and reliable tool to monitor the biochemical effect of hematopoietic stem cell transplantation in Hurler syndrome patients. Bio Blood Marrow Transplant. 2010;16:701-4.

3. Chamoles NA, Blanco M, Gaggioli D, Casentini C. Hurler-like phenotype: enzymatic diagnosis in dried blood spots on filter paper. Clin Chem. 2001;47(12):2098-102.

4. Good Epidemiological Practice (GEP) proper conduct in epidemiology research – IEA European Federation (November 2007).

4.2 PUBLICATIONS/ABSTRACTS OF THE REGISTRY RESULTS

Not applicable.

4.3 PUBLICATIONS CITED IN THE REFERENCE LIST

See Appendix 4 Publications