U.S. FOOD & DRUG ADMINISTRATION

Our Reference: [redacted]

MEETING SUMMARY
October 15, 2018

[redacted]

Dear [redacted]

Attached is a copy of the memorandum summarizing your September 18, 2018, pre-IND teleconference with CBER. This memorandum constitutes the official record of the teleconference. If your understanding of the teleconference outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER as soon as possible.

Please include a reference to [redacted] in your future submissions related to the subject product.

If you have any questions, please contact [redacted].

Sincerely,

[redacted]

Meeting Summary
(Includes Preliminary Meeting Responses)

Meeting ID #:	[redacted]
Submission type & #:	
Product name:	Recombinant serotype 9adeno-associated virus vector (AAV), encoding a codon-optimized human SUMF1 transgene
Proposed indication:	Treatment of multiple sulfatase deficiency (MSD)
Sponsor:	[redacted]
Meeting type:	Type B
Meeting category:	Pre-IND
Meeting date & time:	September 18, 2018, 1:05 p.m. – 1:58 p.m., EDT
Meeting format:	Teleconference
Meeting Recorder/RPM:	[redacted]
Preliminary Responses:	September 16, 2018

FDA Attendees:

[redacted]

Sponsor Attendees:

[redacted]

Background and Objectives:

The sponsor submitted a meeting request on June 29,2018, to discuss the nonclinical and clinical development of AAV9/SUMF1 and to seek FDA guidance on the proposed IND-enabling nonclinical efficacy and safety studies, manufacturing, and the proposed clinical trial design. The pre-meeting materials were submitted on August 16, 2018.

FDA provided its preliminary meeting responses to the sponsor's questions on September 16, 2018. After reviewing the preliminary meeting responses, the sponsor notified FDA on September 17, 2018, of its decision to limit the meeting to discuss only question numbers 6, 7, 8, and 10 and Additional FDA Questions/Comments 1a and 1f.

Sponsor Questions:

Preclinical

Sponsor Question 1:
Does the agency agree that the proposed GLP rat toxicology study, along with our non-GLP mouse studies, are sufficient to support the safety of AAV9/SUMF1 in the proposed Phase I/II clinical trial?

FDA Preliminary Meeting Response to Question 1:
Based on the information provided in Section 4.7 of your pre-IND package, we tentatively agree that your proposed GLP rat toxicology study and non-GLP mouse studies may be sufficient to support the safety of *AAV9/SUMF1* for the proposed clinical trial. Please note that our current position is contingent on your satisfactory response to the following comments, and a final determination will made following our review of comprehensive material, including complete study reports, in your IND.

1. Regarding your GLP toxicology study:

    a. Please include organ weight assessment for a more comprehensive list of organs including the brain, spleen, adrenal glands, thymus and testes.

    b. For all unscheduled deaths, please perform comprehensive clinical pathology, gross pathology and histopathology on a complete list of tissues, and other analyses, as appropriate, in order to determine the cause of death.

2. Please provide your method of dose level extrapolation from each animal species used to humans. Additionally, please include your rationale, with supporting data, for this method. If cerebrospinal fluid (CSF) volume or brain weight is used in your dose extrapolation method, please provide a tabulated summary of values for neonatal, juvenile and adult animals used in your preclinical proof-of-concept (POC) and safety studies, in addition to the corresponding values for human pediatric subjects.

3. For your intrathecal route of administration, please include details pertaining to the accuracy and reproducibility of your administration procedure in the animal models used.

4. Please include a tabulated summary of the similarities and differences between preclinical and clinical vector lots, including vector titer, proportion of empty to full capsids, formulation, production site, and overall manufacturing process. Please note that the dilution buffer, container, and delivery device should reflect what will be used clinically, as feasible.

Meeting Discussion for Sponsor Question 1:
FDA agreed that the 90-day study duration for the GLP rat study is likely sufficient, but they would also want to see the longer-term safety data from the murine studies.

Sponsor Question 2:
Does FDA/CBER agree that the completed and planned efficacy studies provide sufficient evidence of benefit to justify the initiation of a Phase I/II pediatric clinical trial?

FDA Preliminary Meeting Response 2:
Based on the information provided in Section 4 of your pre-IND package, we tentatively agree that your completed and proposed POC mouse studies may provide sufficient information to demonstrate the prospect of direct benefit (21 CFR 50 § 50.52) for pediatric study subjects in your proposed clinical trial. Please note that our current position is contingent upon your satisfactory response to the following comments regarding your POC studies.

1. On page 22 - 23, you note significant changes in the purification processes used for your research grade vector lots for your POC studies (UNC) and the toxicology study/clinical lots (UTSW). These changes may impact the proportion of empty to full capsids, potentially affecting the safety and activity profile of your vector. Therefore, we recommend that you conduct a bridging study to compare the activity of your UNC research lot and UTSW toxicology vector lot to support your starting clinical dose level for pediatric subjects in your planned clinical trial. Alternatively, you may consider including an additional group administered the UTSW toxicology lot in your proposed POC study.

2. In Section 4.1 you describe two mouse models for multiple sulfatase deficiency (MSD), JR30711 and JR31625. In your IND, please provide a comprehensive discussion, with supporting data and references, on the biological relevancy of each animal model used in your preclinical development program to the proposed subject population. Your discussion should include, but is not limited to: (a) the onset and progression of the abnormal histopathological and behavioral phenotypes observed in the model; (b) the lifespan of the model; (c) the similarities and differences between the model and humans with MSD (i.e., pathophysiology, biochemistry, functional changes, immune responses etc.); (d) the timing of administration relative to disease progression in the proposed subject population; (e) description of anatomy and physiology of the injection site and the delivery methods in animals versus humans; and (f) the activity of the expressed transgene in the model.

3. Please provide justification for the dose levels, routes of administration, study endpoints (e.g., behavioral, neurological and molecular analyses), timing of assessments, and sacrifice timepoints used in each POC study. Please note that your starting clinical dose levels should be supported by your preclinical studies demonstrating the activity and safety of *AAV9/SUMF1*.

4. We have the following specific comments regarding your proposed POC studies:

   a. Please ensure that all attempts are made to minimize potential study bias, including: i) inclusion of appropriate control groups; ii) randomized assignment of animals to study groups; iii) appropriate staggered dosing of animals across groups; and iv) masked assessment of selected in-life and post-mortem parameters by qualified personnel.

   b. In Section 4.6.2, you state that "brain, spinal cord, liver, kidney, heart, lung, spleen, pancreas, gonad and muscle will be collected and snap frozen for measurement of arylsulfatase A (ARSA), arylsulfatase C (ARSC), and iduronate-2-sulfatase (IDS) sulfatase activities."

      i. Please provide a discussion regarding the relevance of the proposed tissues to be harvested and the specific sulfatases that will be measured.

      ii. Please provide the methodology used to determine sulfatase activity.

   c. Please clarify which tissues will be evaluated for the reduction of accumulated GAG storage.

   d. Regarding the behavioral testing performed, please provide a detailed methodology for each test to verify the objective and stringent nature (i.e. masked assessors, appropriate controls, etc.) of the testing procedure and resulting data interpretation.

5. Please also see our responses to Question #1 Comments #2-4.

Meeting Discussion for Sponsor Question 2:
There was no discussion of this question during the meeting.

Sponsor Question 3:
Does the agency agree that sufficient information already exists regarding AAV9 vector biodistribution to support the use of AAV9/SUMF1 in the proposed Phase I/II clinical trial?

FDA Preliminary Meeting Response to Question 3:
Based on the limited information provided on page 29-31 of your pre-IND package, we tentatively agree that additional biodistribution studies are not needed to support the use of *AAV9/SUMF1* in the proposed clinical trial. However, please note that our current position is contingent upon your satisfactory responses to the following comments.

   a. In your IND, please provide comprehensive data and/or references to support the *in vivo* biodistribution profile of *AAV9/SUMF1*. Please note that reference to preclinical studies included in other regulatory submissions submitted to

the FDA requires a letter from the holder of the regulatory file granting the FDA access to the file in support of your IND submission. (21 CFR 312.23(b))

b. In a tabulated summary, please specify the routes of administration, dose levels, animal species, and the product evaluated (vector, promotor, transgene, etc.) in each study. Please provide a discussion regarding any differences and their impact on the relevance of the referenced data to your clinical product.

Meeting Discussion for Sponsor Question 3:
There was no discussion of this question during the meeting.

Chemistry, Manufacturing, and Controls (CMC)

Sponsor Question 4:
Does the agency agree that the proposed cGMP manufacturing process to be performed at UTSW (figure 9) is suitable to support the Phase I/II clinical study and product development?

FDA Preliminary Meeting Response to Question 4:

1. The manufacturing process appears suitable to support the proposed Phase I/II clinical study. However, the final decision will be made upon an evaluation of all the information contained in the IND. Please provide a detailed description of the manufacturing process in your IND. For additional details on the CMC information necessary to include in your IND please refer the FDA Guidance for FDA Reviewers and Sponsors *Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs),* which is available at the FDA website: https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecompliancereg ulatoryinformation/guidances/cellularandgenetherapy/ucm078694.pdf.

2. Please also provide a description of the Quality Unit at the UTSW manufacturing facility, and at any CMO that will be used to manufacture the product for this study (i.e., CMO used to make plasmids, cell banks if different from UTSW). For additional information on Quality Units and controls for Phase 1 studies, please refer to the FDA guidance for industry *CGMP of Phase 1 Investigational Drugs* available at https://www.fda.gov/downloads/drugs/guidances/ucm070273.pdf.

Meeting Discussion for Sponsor Question 4:
There was no discussion of this question during the meeting.

Sponsor Question 5:
Are the assays and strategy proposed for release testing and product characterization acceptable (table 18, 19)?

FDA Response to Question 5:
The AAV9/SUMF1 final product release tests (table 18,19), do not appear sufficient. We have the following recommendations for additional tests to be included as a part of product lot release:

a. We note that your final product formulation has low ionic strength and we are concerned that this may cause aggregation of your vector at very high titer (≥ 1 x1014 vp/ml). Therefore, we recommend that you monitor aggregation of the final product.

b. Please describe the test(s) that will be used to measure the empty and full Capsids in the final product that is listed on the lot release test plan in Table 19.

c. Please develop a robust potency assay that is quantitative and dose-responsive and reflects the biological function of the vector as well as the expressed SUMF1 protein.

Meeting Discussion for Sponsor Question 5:
There was no discussion of this question during the meeting.

Sponsor Question 6:
Does the Agency agree with the proposed stability program (table 20) for AAV9/SUMF1 to support the proposed clinical trial?

FDA Response to Question 6:

a. We note that you do not have acceptance criteria for some of stability tests. Please specify the acceptance criteria for all the stability tests.

b. Please also add a robust potency test as described in 5c in your stability study.

c. We also have concerns regarding the potential for the formation of product aggregates as noted in FDA response 5.a above, and we recommend that you test for aggregates as a part of the stability study

Meeting Discussion for Sponsor Question 6:
The sponsor asked if an in vitro mRNA assay would be an acceptable assay for potency. FDA reiterated that a potency assay should be quantitative and dose-responsive and reflect the biological function of the product, including the transgene. And, that if the assay proposed is an in vitro mRNA assay the sponsor should submit sufficient data correlating the proposed mRNA assay with an in vivo or in vitro functional study of the product.

Sponsor Question 7:
We propose to explore the development of an in vitro potency assay (section 5.4.1) for release and to monitor the stability of the drug product but can't comment at this time whether it will be sufficiently accurate or precise to use for dose calculations. Therefore, we are planning to dose AAV9/SUMF1 according to a quantity of vector genome-containing viral particles. Is this plan acceptable?

FDA Preliminary Meeting Response to Question 7:
Yes, the dose of AAV9/SUMF1 vector should be based on vector genomes (vg) as this is a measure of the active ingredient and, how the product will be administered in preclinical studies.

a. Please provide a complete description of your vector genome quantitation assay in your IND. Please see additional CMC comments below regarding qualification of your vg quantification assay.

b. We recommend that you use the same qualified vg quantification assay for all your clinical and pre-clinical lots to ensure adequate bridging between studies.

c. Minor changes to the assay or operator may produce wide variation in your vg assay results, which in turn will affect the dose. Therefore, we recommend that you compare the quantity of vg using side-by-side analyses for different lots made (e.g., lots for proof-of-concept, toxicology and clinical studies) and thoroughly investigate any discrepancies or unexpected differences.

Meeting Discussion for Sponsor Question 7:
FDA explained that quantitation of SUMF1 mRNA in cultured cells is not an acceptable potency assay for clinical studies intended to support safety and efficacy of the product for BLA. And that a measure of mRNA level is not sufficient to evaluate transgene function. FDA recommended that the sponsor develop an assay (quantitative or semi-quantitative) based on a relevant SUMF1 activity, to support further product development. (See discussion for question 6).

Clinical

Sponsor Question 8:
Does the agency agree with the general design and enrollment criteria of the Phase I/II trial, the dose escalation strategy and route of administration as summarized in the protocol synopsis (section 6.3)?

FDA Preliminary Meeting Response to Question 8:
Although the design of your proposed Phase 1/2 study is generally acceptable, please provide the following changes/clarifications to the protocol in your IND submission:

1. [redacted]

the safety and feasibility of the study intervention. Because your proposed study in children involves more than a minor increase over minimal risk, the additional safeguard under 21 CFR 50, Subpart D, and in particular 21 CFR 50.52 (i.e., such clinical investigations must offer the prospect of direct benefit to the pediatric subjects) apply. Your IND will need to provide sufficient evidence of the prospect of direct benefit to justify conducting the FIH study in children.

Meeting Discussion for Sponsor Question 8(1):
FDA noted that that this disease is rare with less than 50 patients identified in the literature. Nonetheless, FDA recommended that sponsor should make a good faith effort to identify adolescent patients before treating pediatric subjects. FDA further requested the sponsor to explain in the IND submission the efforts they undertook to recruit "older" study participants.

For first-in-human (FIH) studies, if there are adult subjects with the disease, at least a small initial cohort of adult subjects should be enrolled to obtain preliminary data on safety and feasibility, bioactivity, and preliminary efficacy to support enrollment of pediatric subjects. Although we appreciate that patients with this disease do not appear to survive into adulthood, a juvenile form of the disease exists. When possible, clinical studies should be conducted in individuals who can understand and consent to the study procedures and risks. Therefore, we would recommend that you treat two to three adolescent subjects for this FIH study before enrolling younger pediatric subjects.

2. You propose to enroll three subjects into Cohort 1 and six subjects in Cohort 2. We recommend that you consider using a 3+3 design, in which an additional three subjects will be enrolled into Cohort 1 to provide additional safety information in the event of observed toxicity.

3. In the protocol synopsis, you state: "A DSMB will review all labs and safety data from the first subject before the Day 30 procedures on second individual." We assume that this means that the treatment of individual subjects will be staggered by 30 days. Please confirm.

Meeting Discussion for Sponsor Question 8(3):
The sponsor stated that there would be an interval of 60 days between the treatment of the first and second subject within each cohort and a 30-day interval between the treatment of the third and each subsequent subject. There is also a 30-day interval between the initiation of the second dose cohort. FDA acknowledged that such dosing appeared reasonable.

1. In the protocol synopsis, you state: "Infusion will be terminated for evidence of an allergic reaction of grade 2 or greater. Under CTCAE v.4 criteria, anaphylaxis is grade 3 by definition (symptomatic bronchospasm with or without urticaria; allergy-related edema/angioedema, hypotension), and would result in infusion

termination and systemic treatment." This is confusing, as you note in the first sentence of the above-mentioned passage that the infusion will be terminated by a Grade 2 or higher allergic reaction. Please clarify.

2. In your study, you provided stopping criteria within a dose cohort based on development of unacceptable toxicity, defined as the occurrence two or more Grade 3 or higher unanticipated treatment-related toxicities. In the interest of subject safety, please provide specific rules that will result in the suspension/termination of this study.

Meeting Discussion for Sponsor Question 8(5):
FDA requested the sponsor to provide stopping rules for the study subjects and include them in the study protocol.

Sponsor Question 9:
Are the proposed safety and exploratory efficacy outcome measures, based on the known cause and natural history of the disease, acceptable to the Agency?

FDA Preliminary Meeting Response to Question 9:
Your exploratory bioactivity endpoints (e.g., change in urine and CSF sulfatase enzyme activity, reduction in urine and CSF sulfatides and glycosaminoglycans, motor and cognitive function) and your general plan to monitor safety by collecting adverse event (AE) data are reasonable.

Sponsor Question 10:
Since the ratio of central nervous system mass to whole body mass changes with age, the dose will be scaled by age correlated to brain mass ([48, 49, 50], not body weight based. Does CBER agree with both the rationale for dosing based on age (≥ 4 years old), or by approximate brain size (table 23) for subjects < 4 years old?

Meeting Discussion for Sponsor Question 9:
There was no discussion of this question during the meeting.

FDA Preliminary Meeting Response to Question 10:
You propose to dose your investigational product based upon brain mass rather than body weight, citing three references (48-50). However, these references mainly provide information regarding the correlation between brain mass and age, and you have not provided sufficient information to justify the appropriateness of basing the dosing of your product on brain mass. Please provide additional justification, including a summary of preclinical and/or clinical data, for dosing based on brain mass and for the proposed dosing nomogram. An alternative approach that you may consider would be to base dosing on CSF volume.

Meeting Discussion for Sponsor Question 10:
The Sponsor stated that there were no data regarding CSF volume in children <4 years of age and that is why they chose to dose the study subjects based upon the brain mass. FDA requested the sponsor to

conduct a thorough literature search on CNS administration and in the study protocol provide a justification for the dosing nomogram that they select.

Additional FDA Questions/Comments:

Chemistry, Manufacturing, and Controls (CMC)

1. Please provide the following information in your IND:

   a. A detailed description of the qualification protocol (e.g., samples, standards, reference lots, controls evaluated such as operators, reagents, equipment, etc.) of your assay for quantitation of vector genomes, and data for the following assay performance parameters: accuracy, reproducibility, specificity, sensitivity, and linearity. Please be aware that the qualification protocol has to be tailored to the vector AAV9/SUMF1. Failure to submit sufficient information supporting assay suitability will result in your IND being placed on clinical hold.

      Meeting Discussion for Additional FDA Comment 1a: FDA pointed out that based on experience in the field, we are currently recommending that the inter-assay coefficient of variation (CV%) should be ≤ 15% instead of 30% for the AAV concentration assay. There will be a workshop at the FDA on the quantitation of AAV vectors for gene therapy on December 7, 2018. FDA encouraged the sponsor to attend the workshop.

   b. Data showing the stability of AAV9/SUMF1 in the intended clinical formulation and clinical delivery device. Please assess the amount (vg) and activity (IU) of the product following exposure to the clinical delivery device in a manner that mimics the clinical scenario. Please be aware that the study should include tests conducted over the planned dose-range. Failure to submit sufficient information supporting vector stability in the delivery device will result in your IND being placed on clinical hold.

   c. Information on derivation history, vector map, manufacturing, and testing results of all plasmid DNAs to be used for manufacturing AAV9/SUMF1 in your IND submission. We recommend that you fully sequence each plasmid DNA and submit results of sequence analysis, indicating the origin and function of each vector component, and a summary of any differences comparing to the expected sequence.

   d. Data showing that the plasmids manufactured in a multi-use facility with shared equipment such as bioreactors, centrifuges and columns were not contaminated with previously manufactured products. We recommend

that you adhere to the principles of good manufacturing practices and perform a test for the presence of other contaminating plasmids in plasmid preps when these starting materials are received in the FMP manufacturing facility.

e. Information on history, detailed manufacturing process including reagents used, and testing results (certificate of analysis: COA) of the HEK-293 Master Cell Bank and Working Cell Bank in your IND submission.

f. Testing results (COA) of the clinical lot AAV9/SUMF1 in your IND submission. Regarding the drug substance and drug product specifications, we recommend that you provide acceptance criteria for all the tests based on your previous manufacturing experience.

Meeting Discussion for Additional FDA Comment 1f:
Please narrow down the acceptance criteria for your lot release tests using data obtained from your preclinical and clinical lots.

g. Detailed information or SOP on how the product is handled at the clinical site before administration. This information should be consistent with the study conducted to evaluate stability of the product in the delivery device.

2. We note that you have codon-optimized the SUMF1 gene in AAV9/SUMF1. Please provide in your IND the rationale and details (specifics of the nucleotide changes) of the codon optimization strategy. Please comment on any expected changes to folding or immunogenicity that have been evaluated.

3. In your IND, please submit information on the genetic tests that you plan to use for diagnosis of SUMF1 gene mutations, including:

   a. Name, location, and CLIA certification (if applicable) of the diagnostic laboratory(s) used.

   b. Detailed test methodology(s) and/or SOP(s), and information regarding device and reagent qualification at the CLIA laboratory.

   c. Validation level of the diagnostic test(s) for suitability (i.e., accuracy, sensitivity, specificity, reproducibility), if available.

   d. A list of all SUMF1 mutations that can be (or have been) detected using the diagnostic test(s), and a description of all mutations that will be eligible for entry into the trial.

   e. Information regarding QA/QC systems in place, and diagnostic test report sign-off procedure(s) at the CLIA laboratory.

f. A risk assessment detailing the risk to the study population in case of false positive results leading to recruitment of study subjects who may not be eligible for enrolment in the study.

4. For future development and characterization of your product, you should develop an identity test that can distinguish AAV9/SUMF1 capsid from other serotype capsids manufactured in the same facility.

Preclinical

5. Statements regarding the adequacy of any preclinical study to support a particular clinical trial or fulfill a specific regulatory requirement are made based solely on the information provided in your pre-IND meeting package and are considered preliminary. A final determination regarding the adequacy of the studies cannot be made without CBER review of complete materials that should be submitted in the IND.

6. Please ensure that you have adequately addressed all CBER pre-IND comments in your IND submission. Please provide references to sections and pages where your responses may be found.

7. In your IND submission, please provide complete study reports for all preclinical studies used to support the safety and rationale of your proposed clinical trial. These reports should include, but are not limited to: a) a prospectively written protocol and all protocol amendments or a detailed methodology; b) a detailed description of the study design (e.g., description of the test system used, animal species/animal models, control and test articles administered, dose levels, detailed procedures for test article administration (including delivery device description), and collection of all study protocol parameters, etc.); c) results for all parameters evaluated for each animal on study; and d) your analysis and interpretation of the study data.

8. For each toxicology study performed, please provide documentation showing that the study was conducted in compliance with Good Laboratory Practice (GLP) as per 21 CFR Part 58. If the study was not GLP-compliant, as directed by 21 CFR Part 314.50(d)(2)(v), you should provide a brief statement of the reason for the non-compliance in your IND submission. In addition, please specify in the study report any areas that deviate from the prospectively designed protocol and the potential impact of these deviations on study integrity. Each study should: a) be conducted according to a prospectively written protocol, b) performed in as nonbiased a manner as possible, and c) have appropriate record keeping and documentation of all data.

9. We strongly recommend oversight of the conduct of all non-GLP toxicology studies and each resulting final study report by a Quality Assurance (QA) unit/person that is independent of the personnel responsible for the conduct of this study, as per 21 CFR Part 58.35. This QA oversight is important to assure

study conduct according to sound procedures and to ensure the quality and integrity of the resulting data.

10. Please provide a copy of all key publications cited that are used to support the safety and rationale for the use of your investigational product in the proposed clinical trial in the IND submission. Please include a comprehensive summary for each publication. The summary should provide the reason for including the publication (i.e., how it directly supports safety/activity of your product) and a discussion regarding the comparability of the product(s) used in the publication to the final clinical product.

    If you plan to conduct the clinical trial at more than one study site, please provide an Investigator Brochure in the IND submission.For a comprehensive summary regarding the preclinical assessment of cell and gene therapy products, we refer you to: a) the document titled, Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (November 2013), at: https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM376521.pdf; and b) the OTAT Learn Webinar Series at: http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm.

The preclinical program for any investigational product should be individualized with respect to scope, complexity, and overall design, to maximize the contribution and predictive value of the resulting data for clinical safety and therapeutic activity. As recommended in Section III.B.8 of the *Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products*, we encourage you to explore opportunities for reducing, refining, and replacing animal use in your preclinical program. For example, it may be appropriate to use *in vitro* or *in silico* testing to complement or replace animal studies. We encourage you to submit proposals and justify any potential alternative approaches.

Clinical

11. Multiple sulfatase deficiency (MSD) is a rare autosomal recessive lysosomal storage disease, with approximately 40 cases reported in the literature. Given the rarity of the disease, it appears unlikely that it would be feasible for you to conduct a follow-on, randomized, blinded, placebo-controlled study at the completion of this FIH study. In light of this, we recommend that you consider either: a) designing your FIH study to be a randomized, placebo-controlled study; or b) conducting a natural history study in this patient population to generate information that would help select the appropriate study population and clinical endpoints for future studies, as well as improving the interpretation of clinical data collected in the FIH study and subsequent studies.