

**Drug Development in Rare and
Orphan Diseases:
Introductory Comments from
the US Food and Drug
Administration
August 2, 2013**

**Why We Are Here
Working Together
to Develop New Drugs
for Niemann-Pick Type C Disease**

Partnership is the Key

- “Coming together is a beginning; keeping together is progress; working together is success.”

Henry Ford

http://www.brainyquote.com/quotes/authors/h/henry_ford.html

Janusz Korczak (1878-1942), a children's advocate, spoke of a Declaration of Children's Rights long before any such document was drawn up by the Geneva Convention (Korczak: 1924) or the United Nations General Assembly (Korczak: 1959)

A hundred children, a hundred individuals who are people – not people-to-be, not people of tomorrow, but people now,
right now – today

How To Love A Child, Janusz Korczak



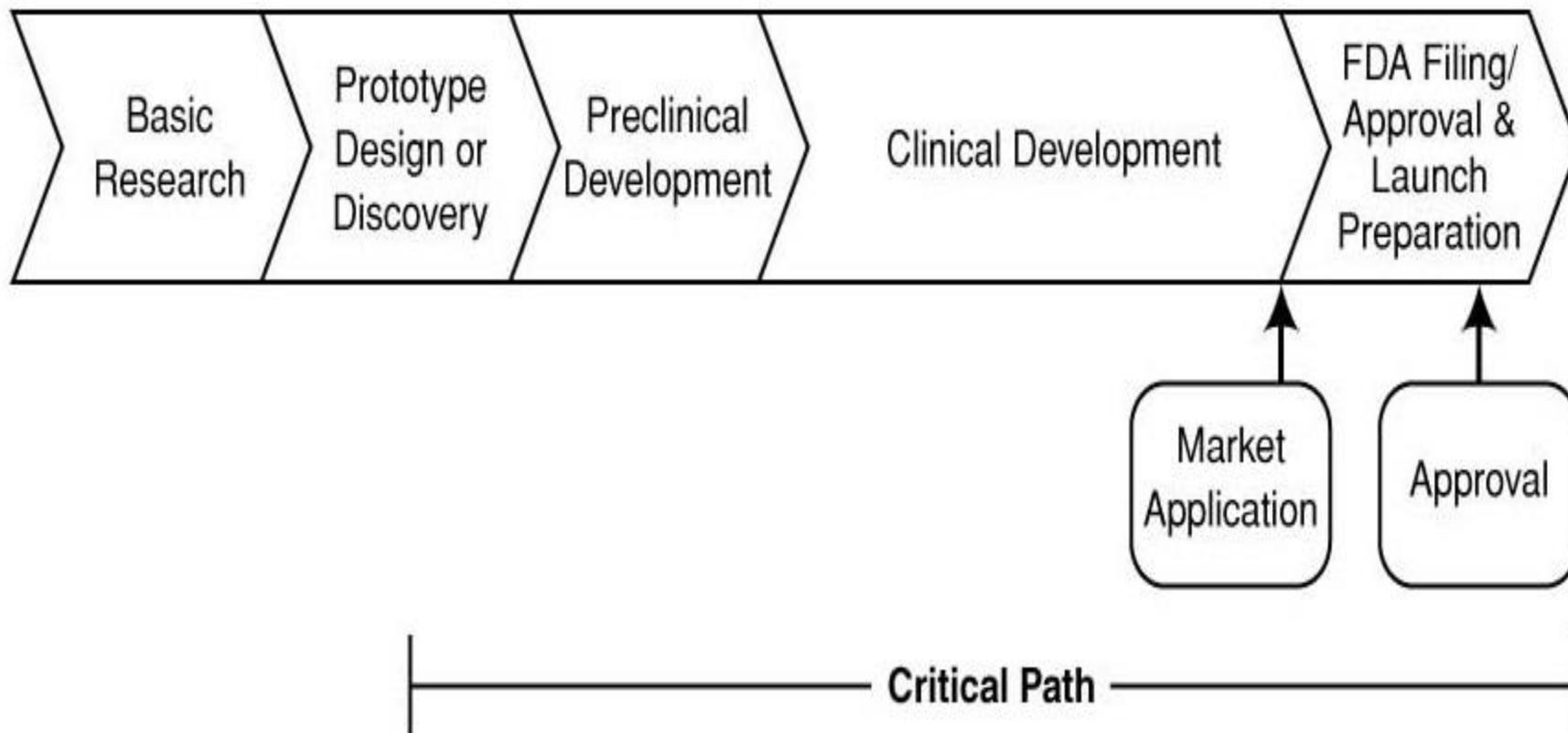
General Principles

Best access to safe and effective treatment is having an approved product on the market

Pathway to An Approved Product

- How do we get there?
- What are the obstacles?
- How can a partnership among stakeholders facilitate achievement of this shared goal?
 - Assist in identification of clinically meaningful, measurable and interpretable endpoints
 - Assist in identifying acceptable designs for trials that can enroll AND answer key questions
 - Share a commitment to completion of a successful drug development program

The Critical Path for Medical Product Development



Clinical Development Challenges for Rare Diseases

- Rare = few patients available for study
 - Makes “getting development right” critical from the start
- Chronic, progressive, serious, life-limiting and life-threatening with unmet medical need
- Many different clinical presentations
- Natural history often not well understood
- Well defined endpoints, outcome measures/tools/instruments, biomarkers can be lacking

Key Objectives of Drug Development

- In addition to assuring a new drug is safe and effective, a drug manufacturer must also:
 - Assure that methods used in manufacturing are adequate to preserve the drug's identity, strength, quality and purity
 - Assure that similar safety and efficacy can be expected with each batch

Clinical Trial Objectives

- Establish that the drug is safe and effective for its proposed use
- Obtain evidence to support drug labeling that guides providers and patients on how to use the drug for patients safely and effectively.

Evidentiary Standard for Approval

- Regulatory Requirement: Demonstrate **substantial evidence of effectiveness/clinical benefit**¹
- Substantial evidence of benefit requires *adequate and well-controlled clinical studies*²
 - Study should be designed well enough “to distinguish the effect of a drug from other influences, such as spontaneous change..., placebo effect, or biased observation”³
 - Usual approval standard is two adequate and well-controlled studies

- ¹21CFR 314.50
- ²21CFR 314.126
- ³ibid.

Adequate and Well-Controlled Study

- Major elements:
 - Clear statement of purpose
 - Identification of subjects for study including:
 - Assignment to treatment/control groups
 - Comparison of active treatment with a control
 - **placebo, no-treatment, active, dose-comparison, historical**
 - Adequate procedures to minimize bias
 - **Outcome measures that are well-defined and reliable**
 - **Analysis of results allows assessment of the drug effect(s)**

Minimizing Bias

- Adequate measures should be taken to minimize bias on the part of:
 - Subjects
 - Observers
 - Analysts of the data
- Examples of procedures to accomplish this include:
 - Randomization
 - Double Blinding

Vulnerabilities to Bias

- Reliance on subjective measurements in the context of an open label study or a study in which there is limited ability to blind
- Retrospective chart review
 - Caregiver who entered the information in chart decides what to record and what not to record
 - Abstractor interprets what was in the chart and may need to “retrofit” clinical descriptions into measurement scales

Historical Controls*

- Usually reserved for special circumstances, for example in:
 - Studies of diseases with high and predictable mortality
 - Studies in which the effect of the drug is self evident

*21 CFR 314.126

Ethics of studying rare diseases

Investigational new drug application

- Clinical research in rare diseases should satisfy the same ethical requirements that apply to clinical research generally. People with rare diseases deserve the same protections.
- Drugs/biologics for rare diseases should meet the same statutory standards of safety and effectiveness that apply to drugs/biologics for more common diseases.
- “FDA has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards while preserving appropriate guarantees for safety and effectiveness.”*

*21 CFR 312.80, Drugs intended to treat life-threatening and severely-debilitating illnesses

“Flexibility”

New drug application for marketing

- Regulations provide room for flexibility*
 - “While the statutory standards apply to all drugs, the many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs demand flexibility in applying the standards”
 - “The FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information....required to provide for a particular drug to meet the statutory standards.”

*21 CFR 314.105(c)

2013* Orphan Drug Approvals

- 17 drug/biologic approvals for orphan diseases
 - 12 by CDER; 5 by CBER
- Of CDER's 12 approvals, 5 were new molecular entities (NMEs) + 7 were repurposed/non-NMEs
- For the period 1983-2010:
 - 135 non-cancer orphan drug NMEs approved
 - Two-thirds relied on only 1 adequate and well controlled study + supportive evidence (usual standard is 2 A&WC studies)**
 - 9 approvals were based on surrogate measures of efficacy

* <http://www.accessdata.fda.gov/scripts/opdlisting/ood/>

**Sasinowski, FJ. Quantum of effectiveness evidence in FDA's approval of orphan drugs. Drug Inf J 2012;46:238-263

Evaluating Treatments for Niemann Pick Disease

Adequate and Well-Controlled Study Design Challenges in NPC

- Heterogeneous clinical presentations (phenotypes)
 - Among patients
 - **Intra-patient** variability in severity of symptoms over time
- Qualitative nature of manifestations
 - Makes it difficult to leverage retrospective chart reviews to obtain natural history
- **Absence of well defined endpoints, outcome measures/tools/ instruments**
 - What degree of change is meaningful?
 - If each patient has a wide range of disease manifestations, what if only one improves or slows in progression but others continue to deteriorate at same rate?

Challenges in Interpreting Treatment Effects in NPC

- Reliance on data from open label, uncontrolled trials, historical-controlled trials, or case series (e.g., compiled individual IND data) requires that the treatment effect be large enough to interpret in the absence of a control
- Interpretation of outcomes in NPC will be challenging if:
 - **The treatment effect is not dramatic**
 - **The effect is a slowing of disease progression with small differences with unclear clinical benefit**
 - **There is substantial inter-patient variability in treatment response**

Ethical Issues with Choice of Control Group

- No known effective treatment exists for NPC
- An “active” controlled trial offers a prospect of direct benefit to all the enrolled children
- A “placebo” controlled trial does not offer a prospect of direct benefit to those children enrolled in the placebo arm
 - Thus, the risks must be no more than a minor increase over minimal risk, precluding placement of an indwelling reservoir.
 - An “unblinded” study (no indwelling reservoir) would solve this issue, but may introduce unacceptable biases.

Federal Register 78(38), 12937- 12951 (02/26/13)

Drug Development Challenges

- Program must be based on a solid scientific foundation
 - Important to have an understanding of the drug mechanism of action and disease pathophysiology
 - Natural history of disease needs to be characterized
- Study design should be based on population under study, and expected drug effects
 - Relapsing remitting vs. chronically progressive
 - Potentially curative vs. improving an aspect of disease
- Substantial evidence of effectiveness can be shown by a single study but results must be statistically persuasive

Drug Development Challenges (2)

- Before initiating pivotal clinical efficacy trials, it is critical to:
 - Map out the clinical development program
 - Conduct a natural history study early in development
 - Design efficient early phase trials to inform the design of pivotal efficacy trial(s)
- Assess safety and tolerability throughout the entire drug development process

How Does Expanded Access Fit into a Clinical Development Program for NPC?

- FDA and stakeholders can work together to achieve an appropriate balance between:
 - Providing access to promising drugs/biologics for patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy
 - While protecting patient safety and avoiding interference with the development of investigational drugs for marketing

How Does Expanded Access Fit into a Clinical Development Program for NPC (2)

- Based on the limited interpretability of uncontrolled individual IND (i-IND) data, these data *alone* are unlikely to serve as the foundation for new drug approval
- Use of a standardized protocol could enhance the collection of information on drug exposure in patients not eligible for the pivotal trial(s)
 - These observational data could provide some support for safety findings obtained in the pivotal trial(s)

Best access to safe and effective treatment is having an approved product on the market

- How do we get there?
- What are the obstacles?
- How can a partnership among stakeholders facilitate achievement of this shared goal?
 - Assist in identification of clinically meaningful, measurable and interpretable endpoints
 - Assist in identifying acceptable designs for trials that can enroll AND answer key questions
 - Share a commitment to completion of a successful drug development program

Important components of a successful drug development program in NPC

- All stakeholders are represented to voice their perspectives
- Protocols include the broadest population of patients with NPC
- Key Clinical Outcomes important to patients must be identified and assessment methodologies for these outcomes must be defined

Vision: Approve Safe and Effective Drugs for NPC Quickly

- *How do we get there?*
 - Establish key components of a drug development program (within scientific and regulatory evidence constraints, which allow for some flexibility) and share a commitment to recognize the roles of:
 - Clinical outcome assessment tools
 - Clinical trials
 - Expanded access individual INDs
 - Expanding the natural history registry to understand disease process and clinical presentation(s)

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And TO the children and adults
and families suffering with
NPC, may progress be made
quickly



Frequently Asked Questions About Expanded Access

- **Expanded access regulations for investigational drugs for treatment use: 21 CFR part 312, subpart I. Effective Oct 2009.**
- **Guidance: Expanded Access to Investigational Drugs for Treatment Use – Qs & As**

Expanded Access

- **When an individual patient IND (i-IND) or single patient IND is submitted to the FDA what factors are considered in making a decision whether to approve the individual patient IND?**
 - **Criteria in 21 CFR 312.305(a) and 21 CFR 312.310(a) must be met**

- **For Expanded Access i-IND, FDA must determine all these conditions are met:**
 - **Potential benefit justifies the potential risk and those risks are not unreasonable in the disease context (312.305(a)(2))**
 - **Patient has serious or life-threatening disease or condition and no other comparable or satisfactory therapeutic options (312.305(a)(1))**
 - **Providing access will not interfere with the drug's development for the use (312.305(a)(3))**
 - **Patient can't obtain the drug under another IND or protocol (312.310(a)(2))**

- **Each request is treated as a unique clinical situation; the risks and benefits are evaluated based on that clinical situation**
 - **Patients with same disease may have different severity of manifestations (different risk/benefit ratio)**
 - **Patients with same disease may have different co-morbid conditions (increases risk)**
 - **FDA may be aware of new safety information that indicates the risk is no longer acceptable in the entire group or specific subgroups**

Expanded Access

- **When an i-IND is submitted to the FDA that matches a clinical trial for the same disease conducted under a “standard” IND, what factors are considered in making a decision whether to approve the individual patient IND?**

i-INDs and Potential for Interference with Clinical Development

- **Regulations state FDA can only approve individual INDs if all the previously described CFR criteria are met, including:**
 - **Providing access will not interfere with the drug's development for the use (312.305(a)(3))**
 - **Patient can't obtain the drug under another IND or protocol (312.310(a)(2))**

i-INDs and Potential for Interference with Clinical Development (2)

- **Examples of circumstances under which an i-IND can be justified when a clinical trial is underway**
 - Patient does not meet eligibility criteria
 - Geographic inaccessibility to the trial
- **In a rare disease, the potential for i-INDs to impede clinical development is substantive**
- **FDA/Stakeholders can work together to balance accessibility (e.g., travel difficulty in neurodegenerative disease) and clinical development**
 - Assure wide geographic distribution of trial centers
 - Design trial with measures that could be documented locally

i-INDs and Potential for Interference with Clinical Development (3)

- FDA and sponsor of the IND clinical trial(s) can work together to monitor accrual to the trial and assess for impact of i-INDs on its completion
- **In the setting of a rare disease, by definition, if families of patients eligible for the clinical trial choose to seek treatment under an i-IND instead, clinical trial accrual will likely be impeded.**

Expanded Access Questions:

- **Does the same FDA review team review the IND clinical trial and the i-INDs that propose to study the same drug?**
 - **YES**

Are i-INDs and IND clinical trials held to different review standards?

- FDA must comply with the IND regulations for both (Criteria in 21 CFR 312.305(a) and 21 CFR 312.310(a) must be met)
- Differences in characteristics of patients enrolled in i-INDs and the IND clinical trial can impact the risk/benefit assessment
 - Different disease severity, different co-morbid conditions
- Size of population taking on risk (individual vs. a group) can impact the risk/benefit assessment

Expanded Access Questions:

- **Are i-INDs and “standard” INDs subject to the same reporting requirements?**
 - Yes
- **If an unexpected safety issue arises in either an i-IND or “standard” IND, how does this affect the other? For example, will a clinical hold in the standard IND result in a clinical hold of the i-IND?**
 - The review team considers the relevance of the safety issue to the other INDs.
 - Factors such as similarity of dose, procedures, and treated population are evaluated. If the risk/benefit is sufficiently comparable between the INDs, both will be placed on hold.

Expanded Access Questions:

- **What medical tests and data collection does the FDA mandate for i-INDs to ensure patient safety?**
 - There is no standard set of tests and data collection for i-INDs because the optimal tests to minimize risk to patients must be considered on a case by case basis, in context of factors, including:
 - **What is known about the drug and its toxicity, including:**
 - At the dose proposed for study
 - In the proposed route of administration
 - **Clinical characteristics of the patient**

Expanded Access Questions:

- **What medical tests and data collection does the FDA mandate for i-INDs to ensure patient safety? (2)**
 - There is always risk, and no measures can “ensure that no harm” comes to the patient. All stakeholders must recognize this when considering how much is actually known about the drug (including the drug’s dose, dose schedule and route of administration)

Expanded Access Questions:

- Are there resources available to assist individuals in preparing and submitting i-INDs?
 - FDA website (see additional resource slide)
 - <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm>
 - <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm113709.htm>
 - CFR Part 312 addresses INDs
 - Subpart A provides general provisions for INDs, including definitions, information on charging for investigational drugs
 - Subpart B includes the IND content and format requirements
 - Subpart C provides information on FDA's administrative actions, including clinical hold
 - Subpart D addresses responsibilities of sponsors and investigators.

Expanded Access Questions:

- **What resources are available to assist families/ individuals to prepare and submit individual INDs (single patient IND) (2)?**
 - **Under certain circumstances the FDA will make a standard “shell” protocol available to investigators**
 - **When it becomes critical to assure consistent measures for safety and data collection**
 - **Frequent requests for use of a drug under i-IND**

Expanded Access Questions:

- **What is the cost to the patient of participating in an i-IND?**
 - FDA does not charge for IND processing and review
 - Investigator/sponsor can submit a request to charge patient for recovery of the direct costs of making the drug available (if unapproved). FDA reviews the request and sends a letter to the investigator/sponsor with its decision. (CFR 312.8 and Guidance: Charging for Investigational Drugs Under an IND Qs & As)
 - For i-IND, direct costs + costs to manufacture or acquire the drug from another source, and costs to ship and handle (e.g., store) the drug

Expanded Access Questions:

- **What is the cost to the patient of participating in an i-IND? (2)**
 - Investigator/sponsor doesn't need FDA authorization to charge for the costs of drug delivery, monitoring, disposables, setup and nursing care.
 - Patients must bear the costs of medical care and the evaluations that must be performed to monitor for safety/efficacy
 - Patients bear the costs of harm incurred from the investigational drug, including medical costs for care for adverse reactions.

Advisory Committee Questions:

- **How does the FDA determine which Advisory Committee will be utilized in an AC meeting for an NDA/BLA?**
 - FDA strives to have necessary expertise for discussion
 - For drugs to treat IEM diseases, FDA has traditionally taken applications to the Endocrine and Metabolic Drugs Advisory Committee (EMDAC)
 - Effort is made to supplement the standing Committee with experts on the condition, efficacy measures relied upon in the clinical trial, and specific review issues identified during the review
 - Input solicited from multiple sources
 - FDA is open to applicant's recommendations on areas of technical expertise critical to include
 - For a major safety issue, FDA may conduct a joint meeting of the EMDAC with the Drug Safety and Risk Management AC

Advisory Committee Questions:

- **Can the applicant and/or clinical trial investigator recommend the Advisory Committee that should be utilized for the AC meeting for an NDA/BLA?**
 - **Yes**
- **If the applicant and/or clinical trial investigator don't agree with the Advisory Committee chosen for the AC meeting, what recourse do they have?**
 - **21 CFR 10.75 provides mechanism for an interested person (including applicant) to obtain formal review of any FDA decision. Issues can be raised to the supervisor of the decision maker. (See also Guidance for Industry and Review Staff: Appeals Above the Division Level)**

NDA/BLA Decisional Process Questions:

- **Under what circumstances would FDA's decision vary from the Advisory Committee recommendation?**
 - FDA relies on advisory committees to provide independent, expert advice on significant scientific, technical, and policy matters. Although these outside experts provide advice to the agency, responsibility for the final action remains with FDA.
 - FDA is required to make approval decisions within the requirements set forth by law and regulations
 - Sometimes AC recommendations do not conform to those requirements

NDA/BLA Decisional Process Questions:

- **Under what circumstances would FDA's decision vary from the Advisory Committee recommendation? (2)**
 - FDA takes into consideration the reasons that individual committee members give for their votes
 - FDA may be aware of information that precludes approval that was not available at the time of the AC or could not be presented in a public forum

FDA NDA/BLA Decisional Process Questions:

- **Is there any recourse to challenge FDA's decision when it varies from the AC recommendation?**
 - Regulations set forth process by which applicants can formally dispute FDA's decisions (CFR 314.103, 314.110 (3), *Guidance for Industry and Review Staff: Appeals Above the Division Level*)
 - Dispute starts at level the decision under dispute was made
 - Process provides for sequential escalation of the dispute to higher management levels, as needed
 - 21 CFR 10.75 provides mechanism for an interested person to obtain formal review of any FDA decision

FDA NDA/BLA Decisional Process Questions:

- **Does approval of a drug in another country (including ex-US approvals based on trials conducted in the US) impact FDA's decision to approve the drug for the same indication in the US? If not, why not?**
 - While FDA takes into consideration whether a drug is approved in another country during its review, the final decision is independent of external regulatory agency decisions and is based on FDA's scientific evaluation of available efficacy and safety data, within the constraints of US law and regulations

FDA NDA/BLA Decisional Process Questions:

- **Does approval of a drug in another country (including ex-US approvals based on trials conducted in the US) impact FDA's decision to approve the drug for the same indication in the US? If not, why not?**
 - FDA can/does contact the external regulatory agency to discuss the ex-US regulatory review/decision
 - FDA examines ex-US post-marketing safety data
 - FDA examines the post marketing trials that were requested by the external agency
 - Consideration is given to what questions those trials are intended to answer
 - Data from these trials might inform the US decision



Back up slides

Examples of Flexibility in Trial Design

Approved Drug	Rare Disease Indication	N	Trial Design
Galsulfase	MPS IV; Maroteaux-Lamy syndrome	38	Randomized, double-blind, placebo-controlled for 24 weeks; followed by single-arm blinded crossover to active treatment
Velaglucerase alfa	Gaucher disease	25	Randomized, double-blind, dose comparison (low dose vs. high dose)

- Designs avoid long-term exposure to placebo, all patients receive active treatment

Examples of Flexibility in Endpoints

Approved Drug	Rare Disease Indication	N	Endpoint
Sapropterin dihydrochloride	BH4-responsive Phenylketonuria	88	Change from baseline in blood phenylalanine levels
Carglumic acid	N-acetylglutamate synthase (NAGS) deficiency	13	Change from baseline in plasma ammonia levels

- Approvals relied upon objective measures of efficacy

Evidentiary Standard for Approval

- Generally means two trials
- One adequate and well-controlled trial with confirmatory evidence (See 1998 guidance: Providing clinical evidence of effectiveness for human drug and biological products)*
 - For example: It may be acceptable to base approval on one large, well-designed multicenter study with robust results for a life-threatening or severely debilitating disease.

* www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078749.pdf

Children with autistic spectrum disorders. I: Comparison of placebo and single dose of human synthetic secretin

S E Levy, M C Souders, J Wray, A F Jawad, P R Gallagher, J Coplan, J K Belchic, M Gerdes, R Mitchell, A E Mulberg

Arch Dis Child 2003;**88**:731–736

Aims: To examine the effect of a single dose of human synthetic secretin (HSS) on behaviour and communication in children with autism spectrum disorder (ASD) using an objective measure of communication and social reciprocity and standardised rating scales.

Methods: Randomised, crossover, double blind, and placebo controlled trial of a single intravenous dose of human synthetic secretin (HSS) 2 CU/kg. The 62 subjects (3–8 years) were assigned to group 1 (saline placebo/HSS) or group 2 (HSS/saline placebo). Diagnosis was confirmed by ADI-R (Autism Diagnostic Interview–Revised) algorithm. Severity of symptoms was rated using the CARS (Childhood Autism Rating Scale). Outcome measures included Communication and Symbolic Behavior Scale (CSBS), Ritvo Real-life Rating Scale, weekly Global Rating Scale (GBRS) by parents and teachers, and daily log of gastrointestinal symptoms. The communication subscale of the CSBS, specifying communication function, reciprocity, and social-affective signalling was videotaped and scored by a blinded, trained observer.

Results: Sixty one children completed the study. After randomisation, there were no significant differences in gender, race, age, and parent and teacher GBRS and Ritvo Scale between the two groups. Compared with placebo, secretin treatment was not associated with significant improvement of CSBS standard scores from baseline to 2 or 4 weeks post-infusion. Five children showed clinical improvement in standard scores: two after HSS and three after placebo. There were no significant changes in gastrointestinal symptoms after HSS or saline placebo.

Conclusions: A single dose of intravenous human secretin is not effective in changing behaviour and communication in children with ASD when compared to placebo.

See end of article for
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Placebo and human synthetic secretin in ASD

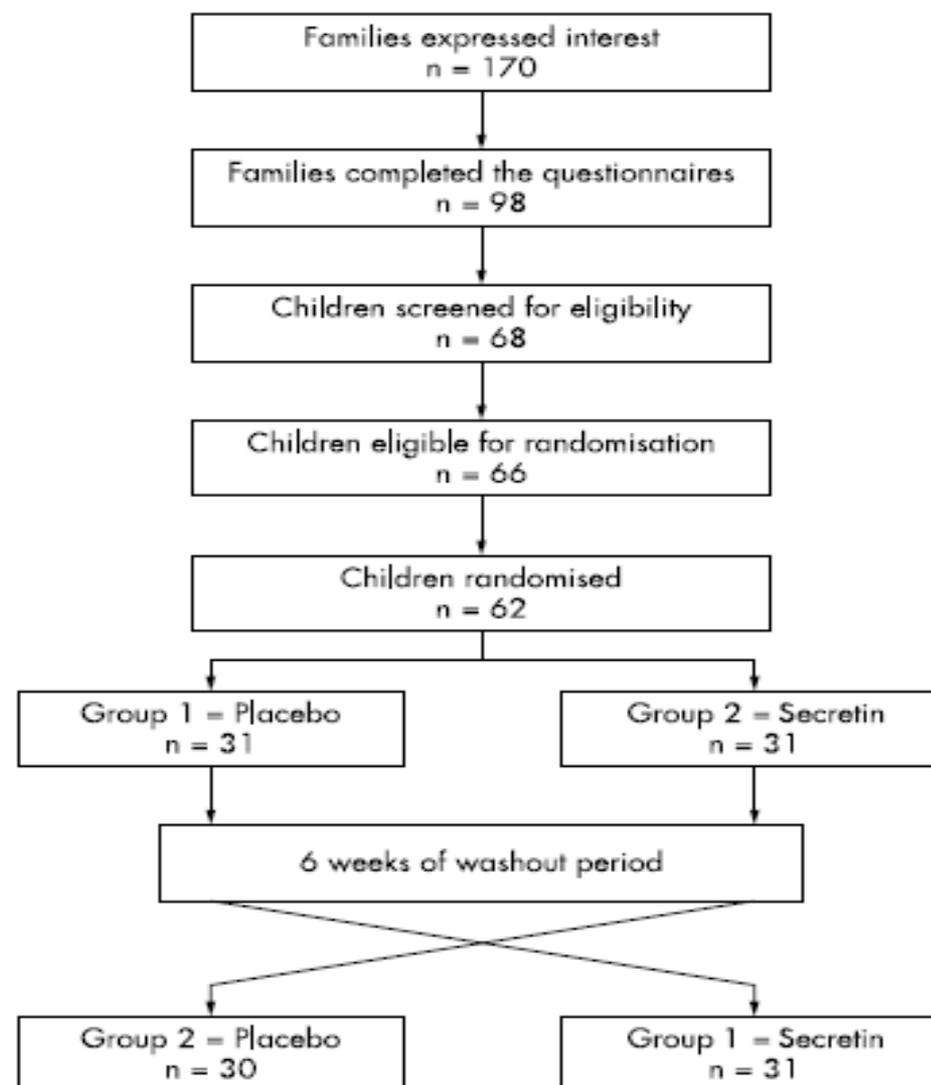


Figure 1 Study design and selection of participants into study.

Experience with Zavesca: AC 1/12/2010

- Major elements of development program:
 - Study 007: controlled and unblinded followed by an uncontrolled extension study.
 - Survey I: a retrospective chart review, uncontrolled;
 - Survey II: retrospective chart review, uncontrolled
 - Case studies, retrospective.
- In light of the safety and efficacy data presented in the application, does the risk/benefit profile of Zavesca support its approval for treatment of Niemann-Pick-C?
 - NO

Choice of Control: Historical Controls

- 21 CFR 314.126 (v): The results of treatment with the test drug are compared with experience historically derived from the **adequately documented** natural history of the disease or condition, or from the results of active treatment, in **comparable patients or populations.**

“Flexibility”

New drug application for marketing

FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards. FDA makes its views on drug products and classes of drugs available through guidance documents, recommendations, and other statements of policy. (§314.105)