CASE STUDIES FROM NEURONEXT

Christopher S. Coffey
Department of Biostatistics
University of Iowa

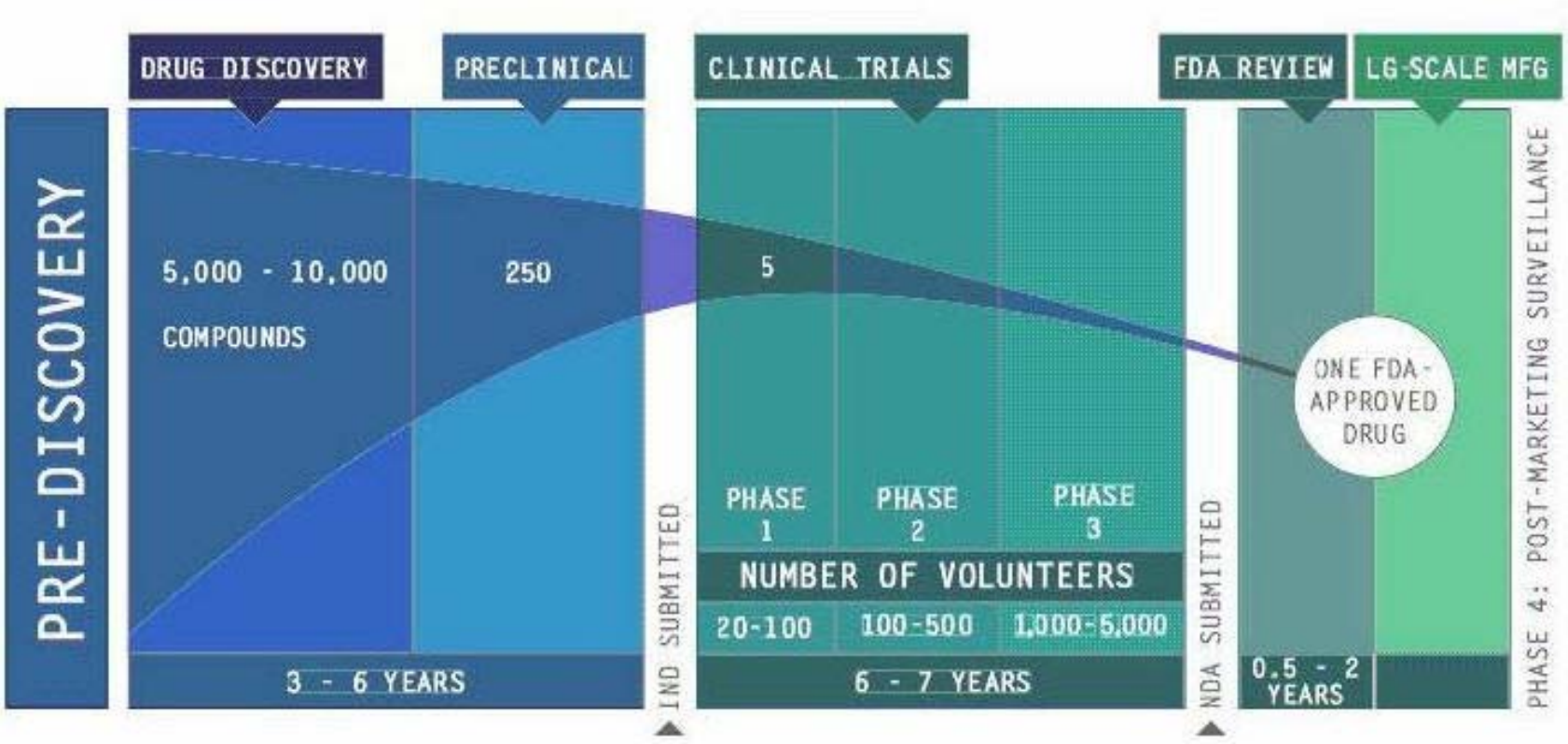
The University of Iowa

The University of Iowa
CT DMC
Clinical Trials Statistical and Data Management Center

OVERVIEW

High levels of risk, uncertainty, & complexity

- Only 11% of drugs that enter clinical testing will be approved in US



Source: PhRMA, 2008

OBJECTIVES

Three basic requirements for any clinical trial:

1) **Trial should examine an important research question**
2) Trial should use rigorous methodology to answer the question of interest
3) Trial must be based on ethical considerations and assure that risks to subjects are minimized

Due to size limitations, meeting these requirements in early phase clinical trials can be a challenge.

As a consequence, the importance of study planning is magnified in these settings.

OBJECTIVES

Fundamental Point:

- Every clinical trial must have one or more primary question(s).
- Should be of interest, and one that is capable of being answered.
- Question on which sample size should be based
- Primary question(s) should be:
  - Carefully selected
  - Clearly defined
  - Stated in advance

OBJECTIVES

Key Aspect - What is the Question?

- Phrase research question in concise, quantitative terms
- Poor Question:

"Is drug A better than drug B"

- Better Question:

"In population W, is drug A at daily dose X more efficacious in reducing Z over a period of time T than drug B at daily dose Y?"

OBJECTIVES

Each objective should link to a primary endpoint(s)

This response variable will be compared across interventions in order to answer the primary question of interest.

Necessary properties:

- Reflects primary objective of trial
- Able to measure in all study subjects
- Specified before trial is started
- As objective as possible

OBJECTIVES

Secondary Objectives:

- Need to be defined a priori (avoid post hoc “fishing expedition”)
- Chosen parsimoniously (avoid false positives)
- Two broad types:
  - Examine response variable different from primary endpoint
  - Subgroup hypotheses

OBJECTIVES

Common Errors in Drug Development:

- Poorly designed and optimistically interpreted “proof of concept” studies
- Insufficient exploration of dose, regimen, and route of administration
- Proceeding to phase III without adequate early phase data to guide study design
  - Population; Sample Size; Endpoints; Study Duration
- Ignoring FDA advice regarding evidence necessary to support a marketing application

PHASE I STUDIES

Phase I Trials:

- First investigation of potential new drug in humans
- Conducted in small number of healthy volunteers
- Results guide dosing and monitoring of future trials
- Objectives:
  - Safety – Assess most significant adverse events
  - Tolerability – Explore possible toxic effects & determine a maximum tolerated dose
  - Pharmacokinetics – Study of how drug is absorbed, metabolized, and eliminated from body
  - Pharmacodynamics – Study of biochemical & physiological effects of drug on body

PHASE I STUDIES

Early learning phase designs in areas with potentially toxic treatments (e.g. cancer/neurological diseases) seek to determine the maximum tolerated dose (MTD).

MTD is highest dose of drug that can be given before some percent of subjects experience an unacceptable dose limiting toxicity (DLT).

If Y denotes binary response with Y=1 denoting occurrence of DLT, and q0 denotes toxicity limit, then we seek to find a dose XMTD where:

$$\Pr(\ Y=1 \mid X_{\mathrm{MTD}}) = q_0$$

PHASE I STUDIES

Accurate determination of the MTD is critical, since it will likely be used as the maximum dose in future clinical development.

- If dose too low, could miss potentially useful drug
- If dose too high, participants in future studies could be put at risk

Generally interested in toxicity values between 10%-40%

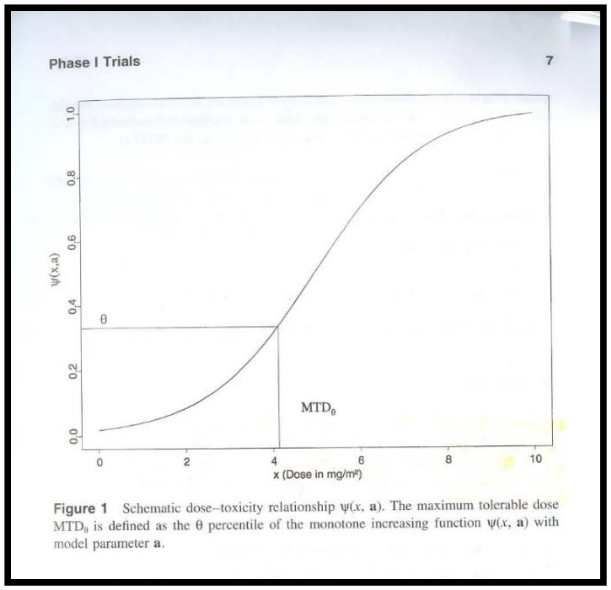


Figure 1 Schematic dose–toxicity relationship $\psi(x, \mathbf{a})$. The maximum tolerable dose MTD_θ is defined as the θ percentile of the monotone increasing function $\psi(x, \mathbf{a})$ with model parameter $\mathbf{a}$.

PHASE I STUDIES

Generally desired to proceed very cautiously:

- Begin with small doses
  - Well below dose expected to cause toxicity
  - But, also likely well below effective dose
- Enroll in small cohorts (1-3 subjects)
- Any given dose escalation cannot increase by more than one level
  - Ethical conflict is to increase dose slowly to avoid unacceptable toxicity, but quickly enough to provide a therapeutic benefit

PHASE I STUDIES

Conventional 3+3 methods, developed for oncology settings, employ an ad-hoc approach to identify MTD.

Subjects are treated in groups of three, starting at initial low dose

Algorithm iterates moving dose up or down depending on number of toxicities observed

The MTD is identified from the data – highest dose studied with less than 2 toxicities out of a maximum of six treated patients.

PHASE I STUDIES

Bayesian paradigm allows incorporating ethical and statistical concerns from pre-clinical studies and sources outside of trial.

- Quantify prior information and uncertainty into a probability distribution
- Update information and easily implement a sequential design strategy
- Use all data to model dose-toxicity curve
- Most common approach is Continual Reassessment Method [CRM – See Garrett-Meyer (Stat Med, 2005) for excellent tutorial]

NEURONEXT NN104 STUDY

Desired Study Parameters:

- Placebo group included for secondary comparison of intracranial bleeding rates
- Enroll approximately 100 subjects
  - 88 subjects in groups of four (3 treated / 1 placebo)
  - Default to placebo during safety review pauses
- Dose limiting toxicities (DLTs) assessed from first dose to 48 hours following last dose of study treatment

NEURONEXT NN104 STUDY

Dose Levels:

- Four dose levels under consideration (dose level can't be increased by > one level at a time)
  - 120 µg/kg
  - 240 µg/kg
  - 360 µg/kg
  - 540 µg/kg

Target Toxicity Rate:

- MTD defined as highest dose with an estimated dose limiting toxicity (DLT) rate of 10% or less

Design:

- Continual Reassessment Method

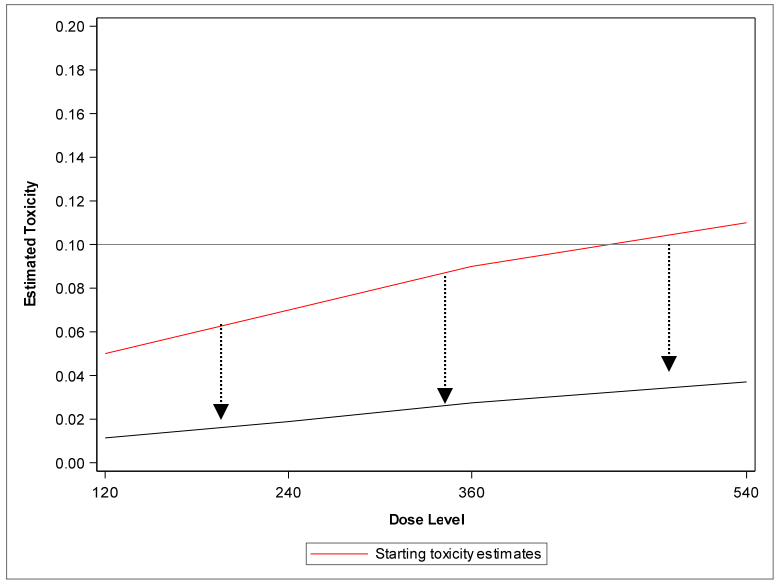
ADAPTIVE DOSE FINDING

CRM model proceeds as follows:

1) Enroll 4 subjects (3 treatment / 1 placebo) into a cohort
2) Determine # of evaluable subjects in cohort
3) Observe # of evaluable subjects (out of 3 treated) that have a DLT per study definition
4) Refit dose-response curve using observed information from all evaluable subjects to date
5) Continue until pre-defined stopping criteria met

NEURONEXT NN104 STUDY

Cohort	Dose (µg/kg)	Evaluable Subjects	# of DLTs	Toxicity Estimates			
				120	240	360	540
				5%	7%	9%	11%
1	120	3	0	1%	2%	3%	4%

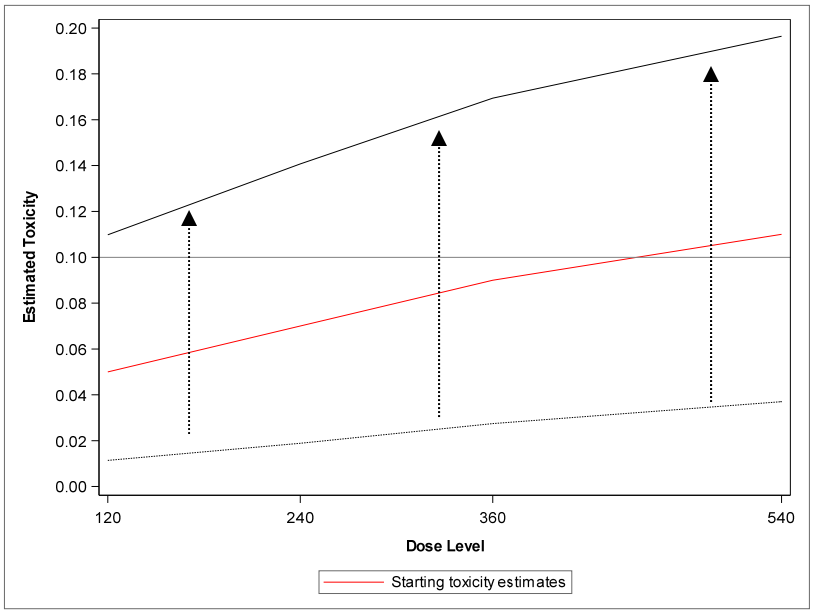


No DLTs observed, estimated curve substantially lower -- all doses < 10%.

But, since dose can only increase by one level, cohort 2 treated at 240 µg/kg

NEURONEXT NN104 STUDY

Cohort	Dose (µg/kg)	Evaluable Subjects	# of DLTs	Toxicity Estimates			
				120	240	360	540
				5%	7%	9%	11%
1	120	3	0	1%	2%	3%	4%
2	240	3	1	11%	14%	17%	20%

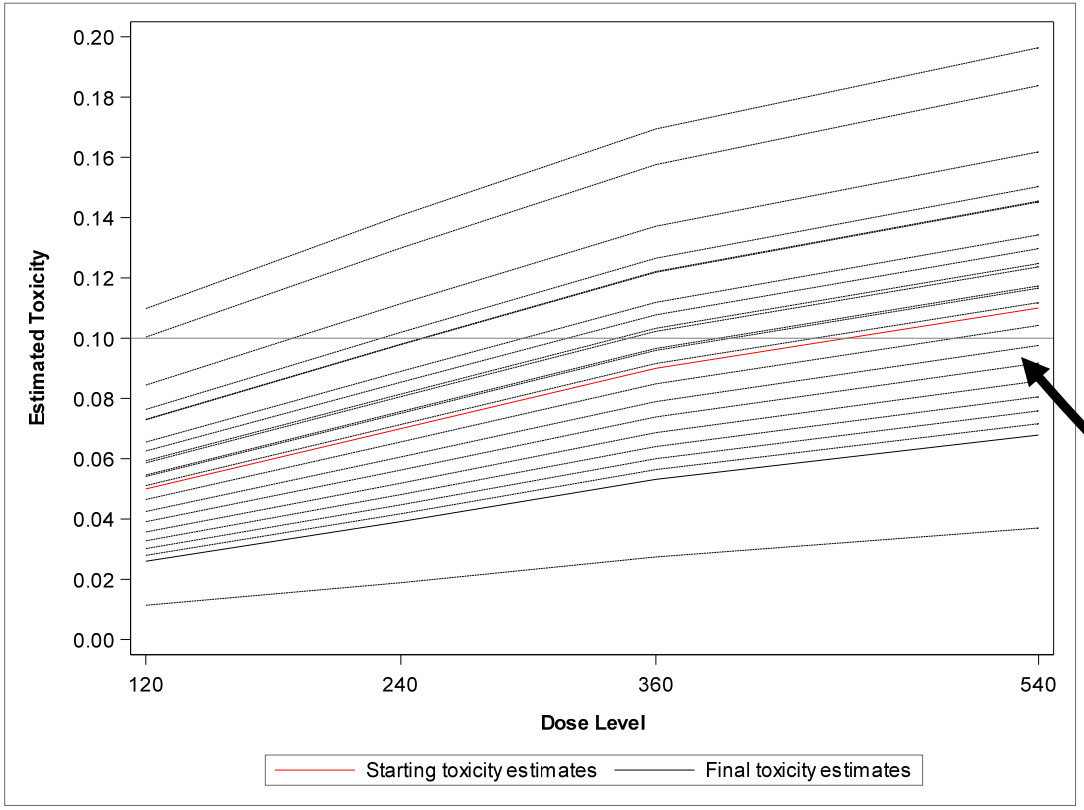


DLT (Cerebral Hemorrhage) observed in subject treated with 240 µg/kg

All DLT estimates now above 10% threshold.

Cohort 3 treated at 120 µg/kg

NEURONEXT NN104 STUDY



540 µg/kg is the maximum tolerated dose, with an estimated DLT rate around 7%

Annals of NEUROLOGY
An Official Journal of the American Neurological Association and the Child Neurology Society
RESEARCH ARTICLE

Final Results of the RHAPSODY Trial: A Multi-Center, Phase 2 Trial Using a Continual Reassessment Method to Determine the Safety and Tolerability of 3K3A-APC, A Recombinant Variant of Human Activated Protein C, in Combination with Tissue Plasminogen Activator, Mechanical Thrombectomy or both in Moderate to Severe Acute Ischemic Stroke

Patrick Lyden, MD,[1] Kent E. Pryor, PhD,[2] Christopher S. Coffey, PhD,[3] Merit Cudkowicz, MD, MSc,[4] Robin Conwit, MD,[5] Ashutosh Jadhav, MD, PhD,[6] Robert N. Sawyer, Jr MD,[7] Jan Claassen, MD,[8] Opeolu Adeoye, MD,[9] Shlee Song, MD,[1] Peter Hannon, MD,[10] Natalia S. Rost, MD, MPH,[4] Archana Hinduja, MD,[11] Michel Torbey, MD, MPH,[11] Jin-Moo Lee, MD, PhD,[12] Curtis Benesch, MD,[13] Michael Rippee, MD,[14] Marilyn Rymer, MD,[14] Michael T. Froehler, MD, PhD,[15] E. Clarke Haley, MD,[16] Mark Johnson, MD,[17] Jon Yankey, MS,[3] Kim Magee, MS,[3]

PHASE II STUDIES

Phase II Trials:

- Performed in patients with disease of interest
- In general, phase II trials may be smaller than they should be
- Results guide design of subsequent confirmatory (phase III) trial

PHASE II STUDIES

- Confirmatory Designs:
  - Large sample sizes
  - Many standard designs

- Learning Stage Designs:
  - Efficiency is critical
  - Carefully evaluate alternative designs

PHASE II STUDIES

Main Goals:

- Provide assessment of preliminary efficacy
  - Screen out ineffective treatments
  - Determine if new treatment is sufficiently promising to justify inclusion in large-scale randomized trials
- Further characterize the safety profile
- **Avoid early phase designs that look to simply be an underpowered phase III study**
  - "Treatment Effects" estimated in pilot studies often tend to be over-estimates of true effect

PHASE II STUDIES

Due to concerns about missing an important effect, researchers may be tempted to include a large number of endpoints.

- If study design often calls for “going forward” if any endpoint shows hint of an effect, then this type of design will almost always “go forward” – even if treatment does not work
- Due to business implications, early phase studies with positive findings are more likely to be highlighted – could be real effect or ‘chance’ finding

PHASE II STUDIES

Due to budgetary constraints, researchers may insist on sample size limitations, regardless of whether there is scientific justification.

- Study may not be able to adequately answer question of interest
- Results become somewhat subjective
  - A researcher who views treatment favorably will likely see positive trends
  - A researcher who views treatment unfavorably will likely see negative trends

PHASE II STUDIES

Types of Phase II Studies:

- Using Different Endpoints Than Phase III Endpoint
  - Safety/Tolerability Designs
  - Surrogate Endpoint Designs
- Using Phase III Endpoints – Not Powered for Efficacy (in Phase III sense)
  - Predictive Probability Designs
  - N-of-1 Designs
  - Selection Designs
  - Futility Designs

SAFETY/TOLERABILITY DESIGN

Possible to design a trial to primarily address safety & tolerability.

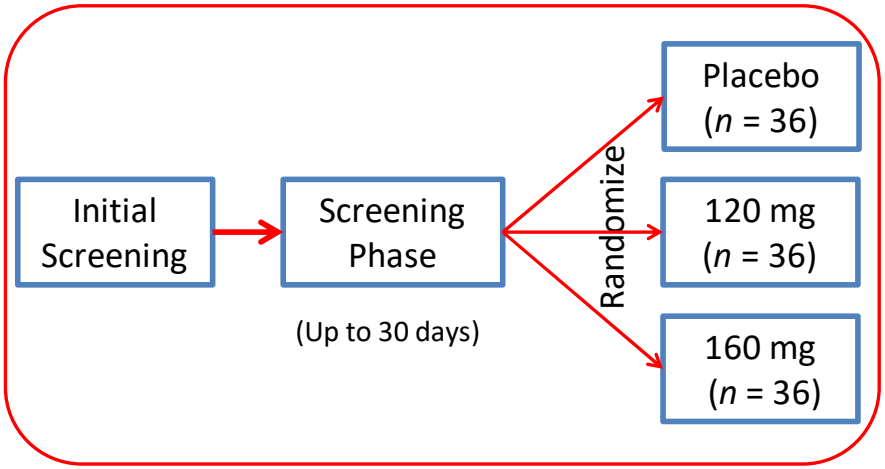
- Trial powered to detect some specified level of safety concerns (usually higher than level of minimal concern)
- Trial also power to detect important differences in tolerability (completing study on assigned dose)
- Efficacy data typically collected as an exploratory outcome

NEURONEXT NN105 STUDY


NN-105 STAIR Study:

- Primary Objective:

  To assess the tolerability of SRX246 in irritable subjects with early symptomatic HD over a period of 12 weeks compared to placebo



NEURONEXT NN105 STUDY

Primary Tolerability Hypothesis:

- Assess whether either 120 mg or 160 mg daily dosing of SRX246 is sufficiently tolerable, compared to placebo.
  - Assessed by comparing percentage of participants enrolled in each dosage group who are able to complete study (12 weeks) on assigned dose
    - Any participant removed from study drug or who fails to complete the study (for any reason) will be deemed not to have tolerated their assigned medication

SURROGATE ENDPOINT DESIGN

As previously discussed, a surrogate endpoint (biomarker) can be measured earlier, easier, and more frequently than many standard clinical endpoints.

A surrogate endpoint design allows using surrogate for ‘go’ / ‘no go’ decision making.

This often leads to reduced sample size or length of study – allowing screening process to move more efficiently.

Subsequent confirmatory studies can still be powered on the gold standard clinical endpoint.

NEURONEXT NN102 STUDY

NN-102 SPRINT-MS Study:

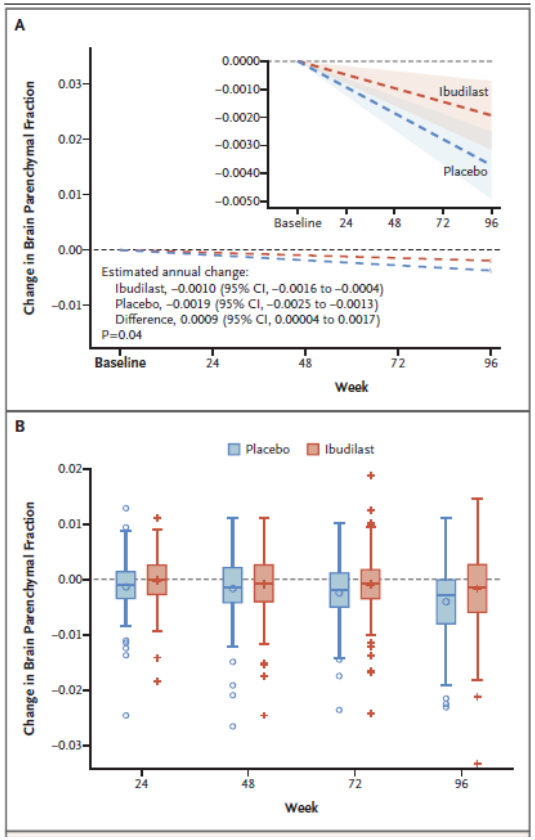
- A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Safety, Tolerability, and Activity of Ibudilast (MN-166) in Subjects with Progressive Multiple Sclerosis
  - PI: Robert Fox (Cleveland Clinic)
  - Primary Objective:

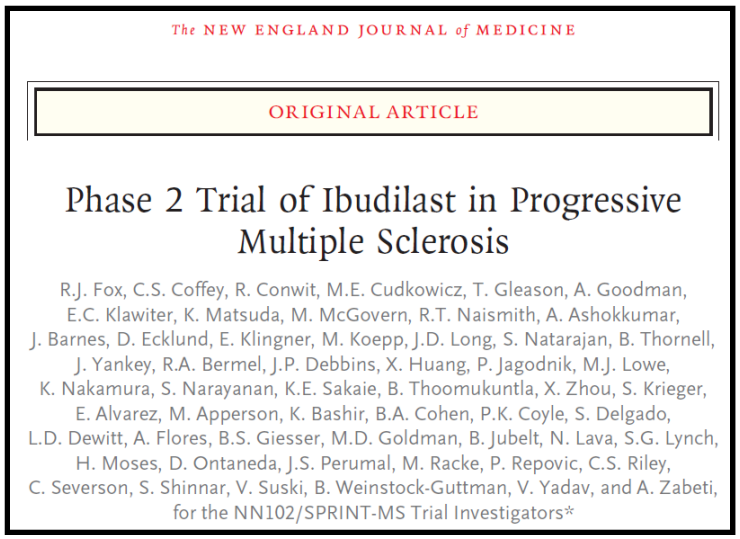
    To evaluate the activity, safety, and tolerability of ibudilast (MN-166 – 100 mg/day) versus placebo administered orally in subjects with primary progressive and secondary progressive multiple sclerosis

NEURONEXT NN102 STUDY

☑ NN102: SPRINT-MS Study

- In a phase 2 trial involving patients with progressive MS, ibudilast was associated with slower progression of brain atrophy than placebo
- Ibudilast was associated with higher rates of gastrointestinal side effects, headache, and depression



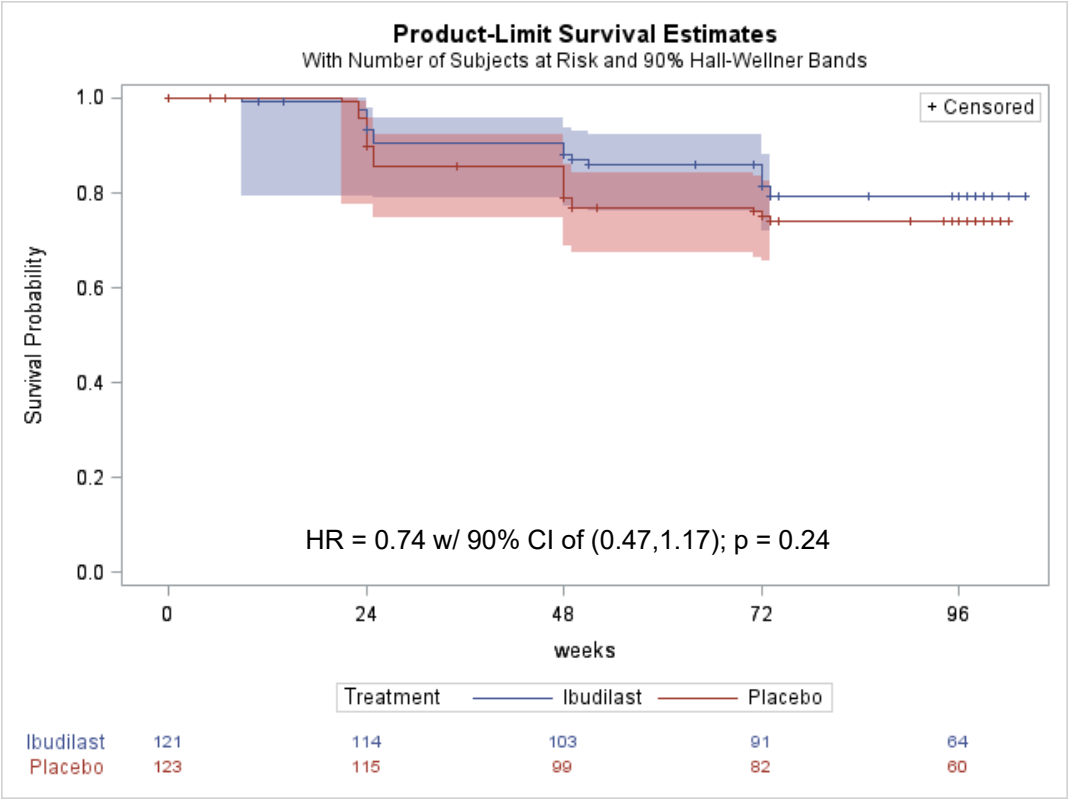

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 2 Trial of Ibudilast in Progressive Multiple Sclerosis

R.J. Fox, C.S. Coffey, R. Conwit, M.E. Cudkowicz, T. Gleason, A. Goodman, E.C. Klawiter, K. Matsuda, M. McGovern, R.T. Naismith, A. Ashokkumar, J. Barnes, D. Ecklund, E. Klingner, M. Koepp, J.D. Long, S. Natarajan, B. Thornell, J. Yankey, R.A. Bermel, J.P. Debbins, X. Huang, P. Jagodnik, M.J. Lowe, K. Nakamura, S. Narayanan, K.E. Sakaie, B. Thoomukuntla, X. Zhou, S. Krieger, E. Alvarez, M. Apperson, K. Bashir, B.A. Cohen, P.K. Coyle, S. Delgado, L.D. Dewitt, A. Flores, B.S. Giesser, M.D. Goldman, B. Jubelt, N. Lava, S.G. Lynch, H. Moses, D. Ontaneda, J.S. Perumal, M. Racke, P. Repovic, C.S. Riley, C. Severson, S. Shinnar, V. Suski, B. Weinstock-Guttman, V. Yadav, and A. Zabeti, for the NN102/SPRINT-MS Trial Investigators*

NEURONEXT NN102 STUDY



Trends toward similar benefit on clinical endpoint of disease progression.

Needs to be confirmed in a larger, confirmatory trial

FUTILITY DESIGN

A futility (non-superiority) design is a screening tool to identify whether agents should be candidates for phase III trials while minimizing costs/sample size.

- If “futility” is declared, results would imply not cost effective to conduct a future phase III trial
- If “futility” is not declared, suggests that there could be a clinically meaningful effect which should be explored in a larger, phase III trial

FUTILITY DESIGN

Statistical Properties:

	Null Hypothesis (H_0)	Alternative Hypothesis (H_A)	Rejecting H_0	Type I Error (α)	Type II Error (β)
Usual Design	$\mu_T = \mu_P$	$\mu_T \neq \mu_P$	New Treatment is Effective (Harmful)	Ineffective Therapy is Effective	Effective Therapy is Ineffective
Futility Design	$\mu_T - \mu_P \geq 0$	$\mu_T - \mu_P < 0$	New Treatment is Futile	Effective Therapy is Ineffective	Ineffective Therapy is Effective

FUTILITY DESIGN

- High negative predictive values:
  If “futility” declared, treatment likely not effective

- Low positive predictive values:
  Lack of “futility” does not imply treatment is effective

Thus, futility designs are good at identifying ineffective treatments, but not very good at identifying effective treatments.

However, improvement over running underpowered efficacy trials in phase II or conducting phase III trials as first rigorous test of efficacy for a new treatment.

NEURONEXT NN103 STUDY

- NN-103 - BeatMG
  - **PI:** Richard Nowak (Yale)
  - A previous study at Yale demonstrated that ~80% of subjects treated with rituximab achieved at least a 75% reduction in their prednisone dose at 52 weeks
  - **Primary Objective:** Determine whether large benefit observed in prior Yale study can be refuted in a multi-site trial, or looks promising enough to justify a future phase III trial (“go”)

NEURONEXT NN103 STUDY

Suppose a 30% increase in favorable response rates (achieving a 75% reduction in prednisone dose) with rituximab over placebo is clinically meaningful.

This futility design tests the following hypothesis:

H_0: Rituximab improves outcome by at least 30% compared to placebo
($p_R - p_P \geq 0.30$ – not futile)

versus

H_A: Rituximab does not improve outcome by at least 30% copmared to placebo
($p_R - p_P < 0.30$ – futile)

NEURONEXT NN103 STUDY

Power to declare "futility" for range of true response rates for rituximab (assumes placebo rate of 40%):

Rituximab Rate (p_R)	30%	35%	40%	45%	50%	60%	70%	80%	90%
Pr (Futility)	92%	84%	74%	63%	50%	25%	10%	2%	<1%

Table demonstrates benefits of using futility design, if true rituximab success rate:

- Near/below placebo rate, declare "futility" with high probability
- Well above placebo rate, low probability of declaring "futility"
- In between, uncertainty to address in subsequent trial

NEURONEXT NN103 STUDY

	Reduction in Mean Daily Prednisone Dose ≥ 75%		1-Sided Odds Ratios (90% CI) Rituximab vs. Placebo
Group	**Rituximab**	**Placebo**	
Primary	60%	56%	1.14 (0 , 2.41)
Observed	65%	63%	1.11 (0 , 2.43)

Primary results show "futility" for showing pre-defined clinically meaningful difference with rituximab (p = 0.03).