USING NATURAL HISTORY DATA AS A COMPARATOR IN AN ULTRA-ORPHAN DISEASE INDICATION

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OUTLINE

1. Ultra-rare Disease Setting: CLN2 Disease and the Clinical Development plan
2. Obtaining Breakthrough Therapy Designation (BTD)
3. BLA submission and discussions concerning retrospective NH data
4. Summary and Conclusions

ULTRA-RARE DISEASE SETTING: CLN2 DISEASE AND THE CLINICAL DEVELOPMENT PLAN

CLN2 DISEASE: CLINICAL PROGRAM PLANNING

Challenges	Advantages
Ultra-rare • Only small N trials viable • Difficult to commit with limited evidence/POC	Potential high efficacy (Δ) • Enzyme replacement therapy • Severe disease, rapid progression
Few Publications	Active scientific community (DEMCHILD) • Existing NH database (N ~ 70)
No validated endpoints	Developing measures of motor & language • Within NH database

NATURAL HISTORY OF CLN2 DISEASE: CHILDREN DECLINE ~2 POINTS PER YEAR IN MOTOR-LANGUAGE SCORE

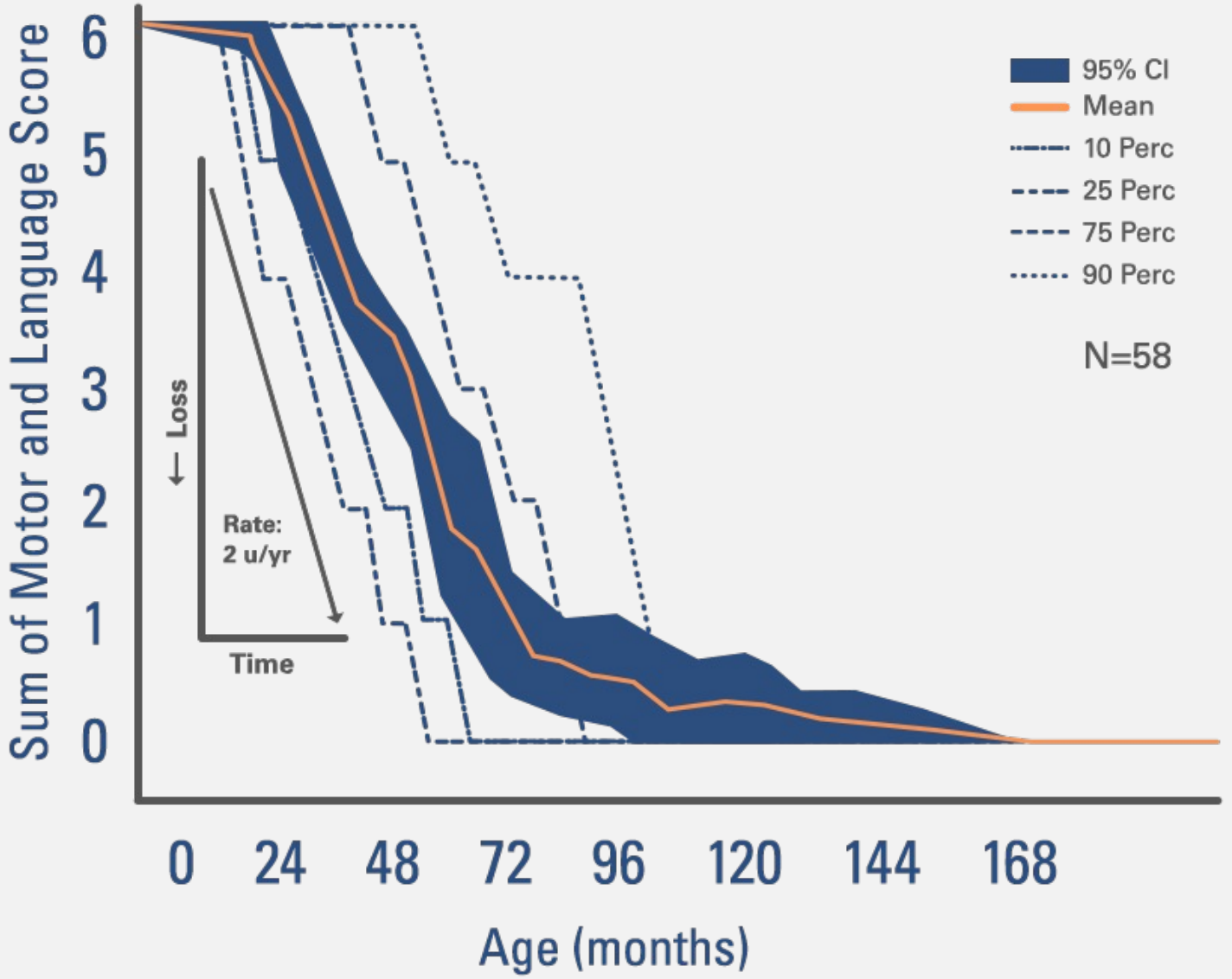
MOTOR and LANGUAGE Assessments

Normal
= 3

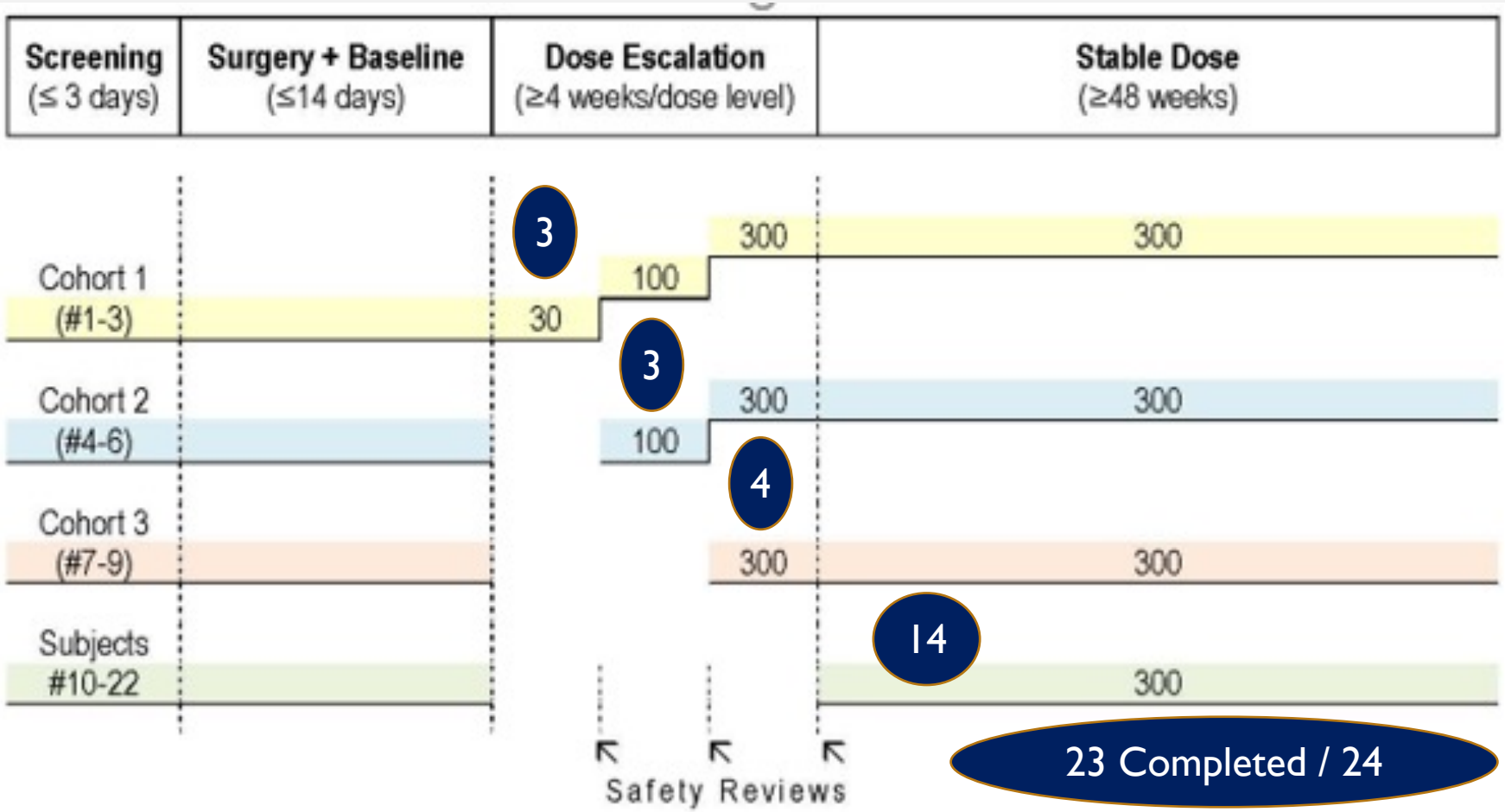
Abnormal
= 2

Poor =
M + L {0 – 6}

No function
= 0



CLINICAL DEVELOPMENT PLAN



A Phase 1/2 Open-Label Dose-Escalation Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Efficacy of Intracerebroventricular BMN 190 in Patients with Late-infantile Neuronal Ceroid Lipofuscinosis (CLN2) Disease

CLINICAL DEVELOPMENT PLAN

Treated Population: Early and active:

- Screening age ≥ 3 years
- Screening ML score in the range 3 – 6

NH Population (Evaluable: N = 42)

- age ≥3 years
- ≥2 ML scores, range 1 – 5, at least 6 months apart

Primary Endpoint: Mean slope of ML score

- CSR: 1-sample T-test – Compare against fixed value “2”
- ISE: 2-sample T-test – Treated versus NH (no matching)

CLINICAL DEVELOPMENT PLAN

Look for early efficacy → negotiate with FDA

- Breakthrough Therapy Designation
- BLA filing on interim data

High Motivation	- dog models very promising - NH data available - High Δ (3 year ML depletion) - ERT in severe disease

OBTAINING BREAKTHROUGH THERAPY DESIGNATION (BTD)

BREAKTHROUGH THERAPY DESIGNATION (BTD)

Objective – develop evidence needed to support approval – efficient as possible

Requirements – early clinical evidence drug provides substantial improvement on **clinically significant** endpoint

1. Effect on irreversible morbidity/mortality or severe symptoms
2. Effect on surrogate/intermediate endpoint likely to predict clinical benefit

Benefits

1. Efficient clinical development (all fast track benefits)
2. Intensive guidance as early as Phase I
3. Organization commitment involving senior managers

BTD – DATA LOOKS

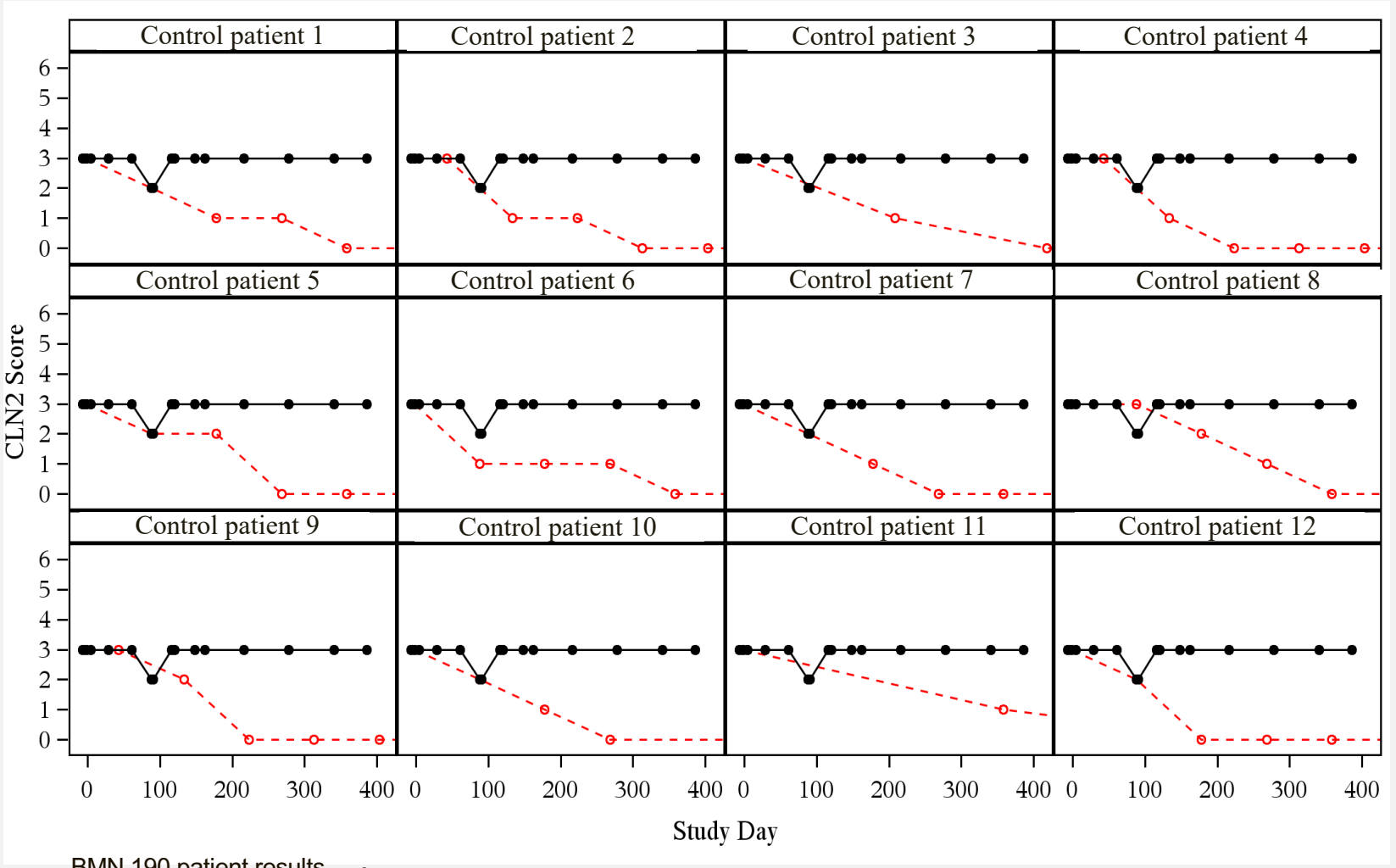
Look #1: 8 of 9 patients treated ≥ 12 months

Treatment: 0%	**NH: 50%**	**P < 0.01**

Month	2-point ML Response
6	0/9 (0%)
9	1/9 (11%)
12	0/8 (0%)

BTD – DATA LOOKS

Look #1: Trial subject A



BTD – DATA LOOKS

Advice	Action
N and follow-up low	Update to Look #2: (N = 8 → 11)
NH includes retrospective data	Compare retrospective vs prospective
NH schedule less frequent than RX trial	Explore NH data (MMRM slope est.) • LOCF, baseline at diagnosis age
ML scale adapted from NH • Commensurate, PRO/DDT validation?	Plan for NH rater to assess videos of RX-ML assessments using NH criteria
Obtain additional NH databases	One smaller NH database contracted

BTD – DATA LOOKS

Granted BTD

Denied interim data filing → complete the 48 week study

BTD Process Operational Challenges

High statistical & programming workload [Double Load]

- Information requests concurrent with BLA preparation [interim data]
- Requests included SAS datasets & exploratory data analyses

BTD decision needed to be finalized before SAP/CDP discussions

- SAP comments received near BLA filing date – many changes

BLA SUBMISSION & DISCUSSIONS CONCERNING RETROSPECTIVE NATURAL HISTORY DATA

BLA OVERVIEW / TIMELINE

~ 5 years from first scientific meetings to approval

~ 3.5 years from FPI to approval

~ 2.25 years Clinical trial

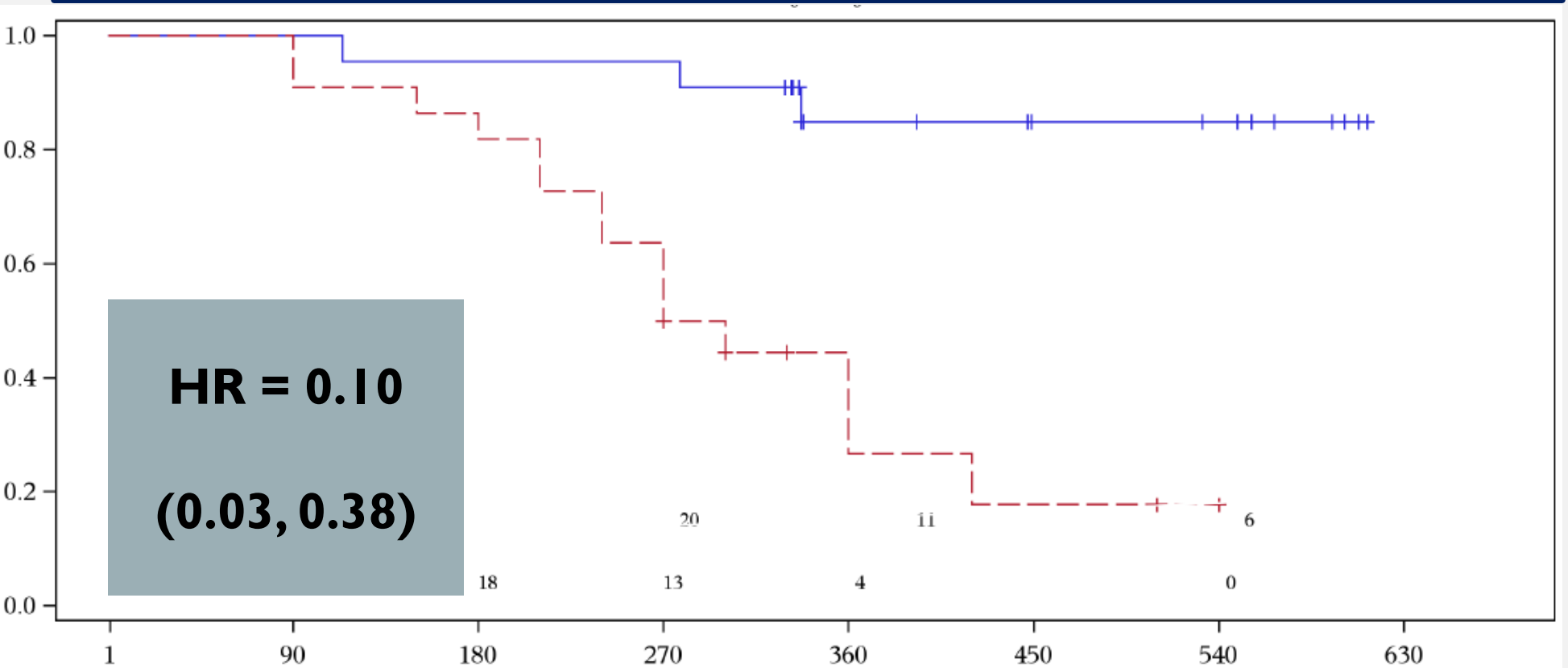
CDP design	Accrual	LPO	DBL to BLA approval
65 Weeks	69 Weeks	48 Weeks	73 Weeks

BLA DISCUSSIONS

Advice/changes generally accepted

- High efficacy seen at time of BLA filing & expedience

Time to ML decline (2-pt drop or zero)



75% slope Reduction (matched)

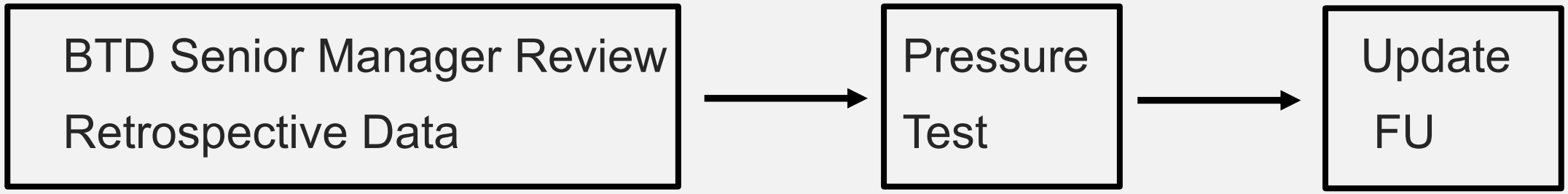
NH	RX
2.06	0.53

BLA DISCUSSIONS

Change	SAP	Pre-BLA changes	Post-BLA changes	
N (24 treated)	N=21: 1 ET X 2 asym X	N=23: 1 ET X 2 asym √	N=22: 1 ET √ 2 asym X	Impute failure
primary endpoint	Primary ML slope • Responder supportive	Responder ML • 2pt drop or 0	Responder M • 2pt drop or 0	Inter-rater (video) questioned L
population / matching	Full population • no matching • N=(42, 24)	Match 1 – 1 • ML, age ≤12 • N=(21, 21)	Match 1 – 1 • ML, age ≤3, gene • N=(17, 17)	Reduced N & power
Analysis method for responder	Fisher Exact		McNemar	R ~ 0
Assessment Schedule		Supportive slopes analysis with LOCF	**All analyses** use LOCF to RX grid	Imputes flatness NH
Generalizability			Cox Models on Full population	
		Consider M.I.		We should have !!

BLA DISCUSSIONS

Many changes!



Updates considered substantial amendment: PDUFA date pushed 3 months

LOCF conservative analyses could only be overcome with updated data

1 – 1 MATCHING

Matching can reduce bias and heterogeneity

- Choose variables predicting ML slope / propensity score matching
- Want high match percentage (age ≤ 12 months apart, equal ML)
- Specify in SAP before first treated follow-up visit

	Mean ML Decline		
Population	**NH**	**Treated**	**Correlation**
Full N = (42, 23)	2.12	0.20	
Matched N = (21, 21)	2.05	0.24	-0.025

We had not planned to match due to no known covariates predictive of disease

LOOKING BACK

Protracted discussion period → Eroded Power

- Simple responder analysis
- Matching (reduced N)
- LOCF

More careful decisions on SAP (ex. Missing data)

- Earlier SAP discussion
- Understand the Regulatory Authority (ex. “why do you ask for MMRM with LOCF?”)
- Drop early BLA file plan / interim data – will not show well with LOCF

LOOKING BACK

Other Lessons

- Use many NH data sources and justify selection
- Own / audit NH data
- Every data point matters when N is small / 100% audit & clean key data
- PRO instruments require validation (or concurrent pilot study).
- Video of assessments is good back-up plan (inter-rater reliability)
- Keep trial endpoints as similar to retrospective NH data as possible (resist improvements)

POWER REVISED ENDPOINTS – PROTOCOL / ISE

If efficacy result not available ?	
Protocol Assumptions	**48 Week Failure Rate**
• 75% Slope Reduction	NH 50%
• NH 2pt loss per 48 Weeks	RX 20%

METHOD	**Not Matched (Full Sample) N=(42,23)**	**1-1 Match BL, age≤12 N=(21,21)**	**1-1 Match BL, age≤3, gene N=(17,17)**	**Impute W.C. For Early Term N=(18,18)**
Fisher Exact	62%	41%	32%	24%

METHOD		**1-1 Match BL, age≤3, gene N=(17,17)**	**Impute W.C. For Early Term N=(18,18)**
McNemer Exact	Assumes pairs not correlated Power loss ~ delete one pair	29%	20%

POWER FOR REVISED ENDPOINTS: ACTUAL

48 Week (protocol)		48 Week (actual)	
NH	50%	NH	51%
RX	20%	RX	9%

METHOD	Not Matched (Full Sample) N=(42,23)	1-1 Match BL, age≤12 N=(21,21)	1-1 Match BL, age≤3, gene N=(17,17)	Impute W.C. For Early Term N=(18,18)
Fisher Exact	62% → 94%	41% → 79%	32% → 66%	24% → 52%
McNemer Exact	LOCF-W48 ↓ power to near 0 Complete FU through Week 96 to overcome LOCF		29% → 61%	20% → 47%

SUMMARY AND CONCLUSIONS

SUMMARY

BLA approved with substantial amendment – extra 3 months

- NH data (exists) & BTD approval likely facilitated (early) BLA approval

Power of original design lost due to concerns non-randomized, non-prospective NH

- Matching reduced N - failed to reduce heterogeneity
- Different schedules (LOCF to W48)

CONCEPTUAL

Randomized 16 x 2 trial has equal power. +10 wks (+23 accrual -13 substantial amd)

- Must assume high efficacy (risk)
- Need NH for assessing longer term efficacy (Control → RX @ W48)
- Treated experience ↓ @ BTD discussions. BTD successful? Necessary?
- Clean and fewer analyses

CONCLUSIONS

Randomized is best, and might not be slower (if high efficacy assumed). Risk?

Prospective >> Retrospective (challenging).

- Link early with Sci. Comm. / academic groups
- Design prospective NH studies / validate endpoints (or semi-validate)

Encourage Sci. Comm. to proceed as if an industry partner is available

- Validate endpoints for regulatory use

Expect high hurdles retrospective NH

- Matching (↓ power)
- Conservative LOCF (↓ power)
- Longer FU ~~[file BLA interim data]~~

Careful Pace (planning):

- Early FDA & **real** discussions
- better endpoints – TTE, recurrent
- Improved imputation from LOCF

THANK YOU !