

WELCOME

BIOMARIN ANALYST AND INVESTOR DAY 2014

Jean-Jacques Bienaimé
Chief Executive Officer

Hank Fuchs
Chief Medical Officer

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Additional Information

The offer by BioMarin to purchase ordinary shares of Prosensa Holding N.V. ("Prosensa") contemplated by the Purchase Agreement, dated November 23, 2014, between BioMarin, Prosensa and BioMarin Falcons B.V. (the "Offer") has not yet commenced. This communication is neither an offer to purchase nor a solicitation of an offer to sell any ordinary shares of Prosensa or any other securities. On the commencement date of the Offer, a tender offer statement on Schedule TO, including an offer to purchase, a letter of transmittal and related documents, will be filed with the United States Securities and Exchange Commission (the "SEC"). Thereafter, Prosensa will file a solicitation/recommendation statement on Schedule 14D-9 with the SEC. The offer to purchase ordinary shares of Prosensa will only be made pursuant to the offer to purchase, the letter of transmittal and related documents filed as a part of the Schedule TO.

INVESTORS AND SECURITY HOLDERS OF PROSENSA ARE URGED TO READ BOTH THE SCHEDULE TO (AND THE INCLUDED OFFER TO PURCHASE) AND THE SOLICITATION/ RECOMMENDATION STATEMENT, AS THEY MAY BE AMENDED FROM TIME TO TIME, AND OTHER RELEVANT DOCUMENTS FILED WITH THE SEC WHEN THEY BECOME AVAILABLE BEFORE THEY MAKE ANY DECISION WITH RESPECT TO THE TENDER OFFER, BECAUSE THEY WILL CONTAIN IMPORTANT INFORMATION ABOUT THE TERMS OF THE OFFER, THE PROPOSED TRANSACTIONS AND THE PARTIES THERETO.

The tender offer statement will be filed with the SEC by BioMarin and the solicitation/recommendation statement will be filed with the SEC by Prosensa. Investors and security holders may obtain a free copy of these statements (when available) and other documents filed with the SEC at the website maintained by the SEC at www.sec.gov or by directing such requests to the information agent for the tender offer that will be named in the tender offer statement on Schedule TO.

2014: BioMarin's Most Productive Year to Date

……..2015 will be more productive

5 Marketed Products to Generate over $700M in 2014 Revenues

Most Diverse Product Pipeline in Orphan-drug Industry

5 Potential Products Currently in the Clinic; 8 in 2015*

Vimizim to Generate ~$100M in First Four Quarters of Sales

Prosensa Acquisition Could Drive Significant Near-term Upside

* 12 including drisapersen and other clinical candidates from Prosensa acquisition

Prosensa Acquisition Highlights

- Great strategic fit and value creator for BioMarin
- Drisapersen has a large body of clinical data that could support early regulatory approval
- Leverages BioMarin's extensive experience getting orphan drugs approved
- DMD is one of the largest monogenetic disorders (approx. 75,000 WW)
- Leverages our global commercial infrastructure and leadership in orphan disease market
- Adds what could be our largest product to a well diversified product portfolio
- With early approvals, accretive to operating and GAAP earnings in 2017
- A potentially transformative investment that is risk managed

Why Prosensa?

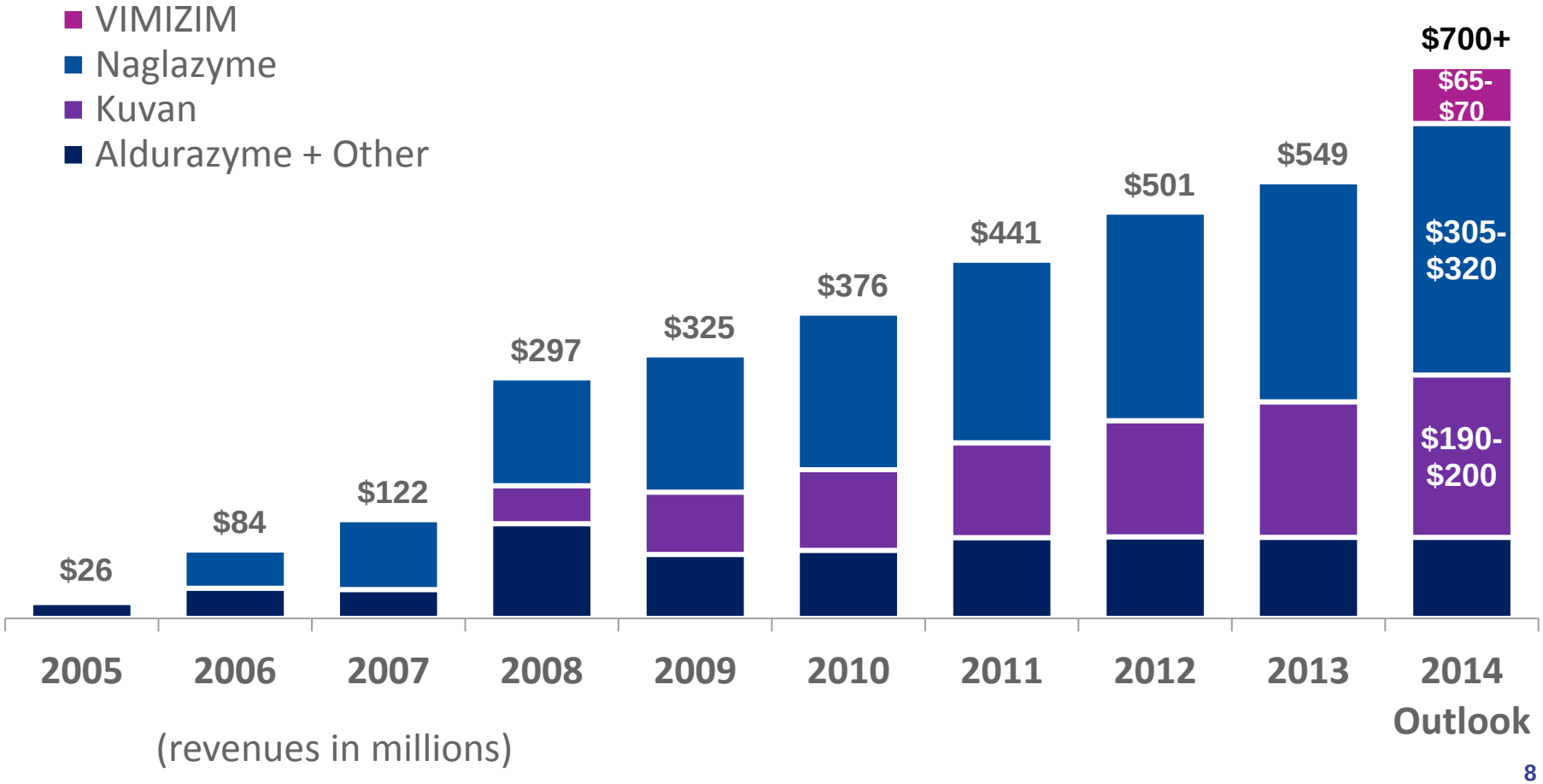
- First to file in the U.S. for the treatment of Duchenne muscular dystrophy
- Our belief that the totality of drisapersen data combined with the significant unmet medical need of this patient population provide a path to early approvals
- Largest data set in DMD comprising three placebo-controlled studies and two long-term open label studies, treating over 300 patients
- New Drug Application (NDA) with Breakthrough Therapy designation currently under rolling review based on existing data; complete NDA submission expected 1Q15; MAA in EMA expected 2015
- In-line with FDA guidance, two confirmatory post-approval studies to support accelerated approval planned to begin 1H15
- Issued U.S. patents through 2023; EU through 2021; potential for extensions
- Low dose that supports sub-cutaneous route of administration
- Anticipated low COGS and available manufacturing capacity to meet market demand

Drisapersen: Timeline of Regulatory Events

- 4Q14 NDA rolling submission commenced with FDA
- 1Q15 anticipated completion of NDA submission with FDA
- 2Q15 expected MAA application for drisapersen with EMA
- 1H15 initiation of two confirmatory studies to support potential accelerated approval for drisapersen

History of Strong Revenue Growth

Core Commercial Products Expected to Continue Growing



(revenues in millions)

What's New Today?

Drisapersen

- Potential near-term registration opportunity in large market with unmet need
- Seamless fit within BioMarin's clinical, regulatory and commercial expertise

BMN 111 for Achondroplasia

- First 3 cohorts enrolled
- Leveraging the natural history study to inform our understanding of our patients and analytic approaches

BMN 190 for CLN2, Late Infantile Form of Batten Disease

- Enrollment completion imminent
- Current study exhibiting excellent safety profile to date

BMN 270 for Hemophilia A

- Launching Phase 1 study 1H15 on track two years after licensing
- Expanded pre-clinical proof of concept to include "real world" (clotting) assays

What's New Today?

PEG PAL for PKU

- Phe lowering in patients from enriched study at 26 weeks is robust at ~60%
- Enhanced strategies in place to facilitate commercialization
- Pivotal data now expected 1Q16

BMN 701 for Late-onset Pompe Disease

- Improved manufacturing process with better purity, potency and COGS
- Modifying program to leverage "to be commercialized process"
- Proof of concept in 20 patients of switch study; enrollment 1Q15/results 4Q15
- Pivotal study resumes 4Q15

Talazoparib for mBRCA BC

- Enrolling more trials, including talazoparib in combination, neoadjuvant, etc.

BMN 250 for MPS IIIB (Sanfilippo B syndrome)

- Launching natural history study with patient accrual expected 2015
- Phase 1 study in MPS IIIB patients 2H15

Agenda and Welcome External Speakers



Cary O. Harding, M.D., F.A.C.M.G.

Professor of Molecular and Medical Genetics and Pediatrics at Oregon Health & Science University

Medical Director of the OHSU Biochemical Genetics Laboratory



Alfried Kohlschütter, M.D.

Expert in NCL disorders (Neuronal Ceroid Lipofuscinoses, Batten disease)

Specialty Clinic for Degenerative Brain Disorders in Children and Adolescents, associated with the Department of Pediatrics, University Medical Center in Hamburg, Germany



Cathleen Raggio, M.D.

Attending Orthopedic Surgeon, Co-Director, The Kathryn O. and Alan C. Greenberg Center for Skeletal Dysplasias at Hospital for Special Surgery, New York



Craig McDonald, M.D.

Professor and Chair, Department of Physical Medicine & Rehabilitation, Center for Healthcare Policy and Research U.C. Davis Children's Hospital

Expert in the clinical management and rehabilitation of neuromuscular diseases including muscular dystrophies and the development of novel outcome measures for clinical trials



Glenn Pierce, M.D., Ph.D.

Expert in the field of hemophilia with more than 20 years of experience

Previously served as the Chief Medical Officer and Senior Vice President of Biogen Idec Hemophilia Therapeutic Area and senior vice president of Hematology, Cell and Gene Therapies at Biogen Idec Inc.



PKU Program Overview – Focus on PEG PAL

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Wolfgang Dummer, M.D., Ph.D.,
Vice President, Clinical Development
BioMarin

PEG PAL Clinical Trial Program

- 1 Phase I and 4 Phase 2 studies have explored initial safety, tolerability, dosing regimens and effect on Phe reduction
- 2 Phase III clinical trials starting 2013
  - 165-301: Open Label Naïve Study (FPI in May 2013)
    - Fixed doses of 20mg/day and 40mg/day
    - Standardized induction/titration regimens to each target doses between 16 and 20 weeks
  - 165-302: Pivotal Randomized Discontinuation Trial (FPI July 2013)

- Extension study 303 for all 301 patients

PEG PAL: Recent Key Changes to Phase 3 Program

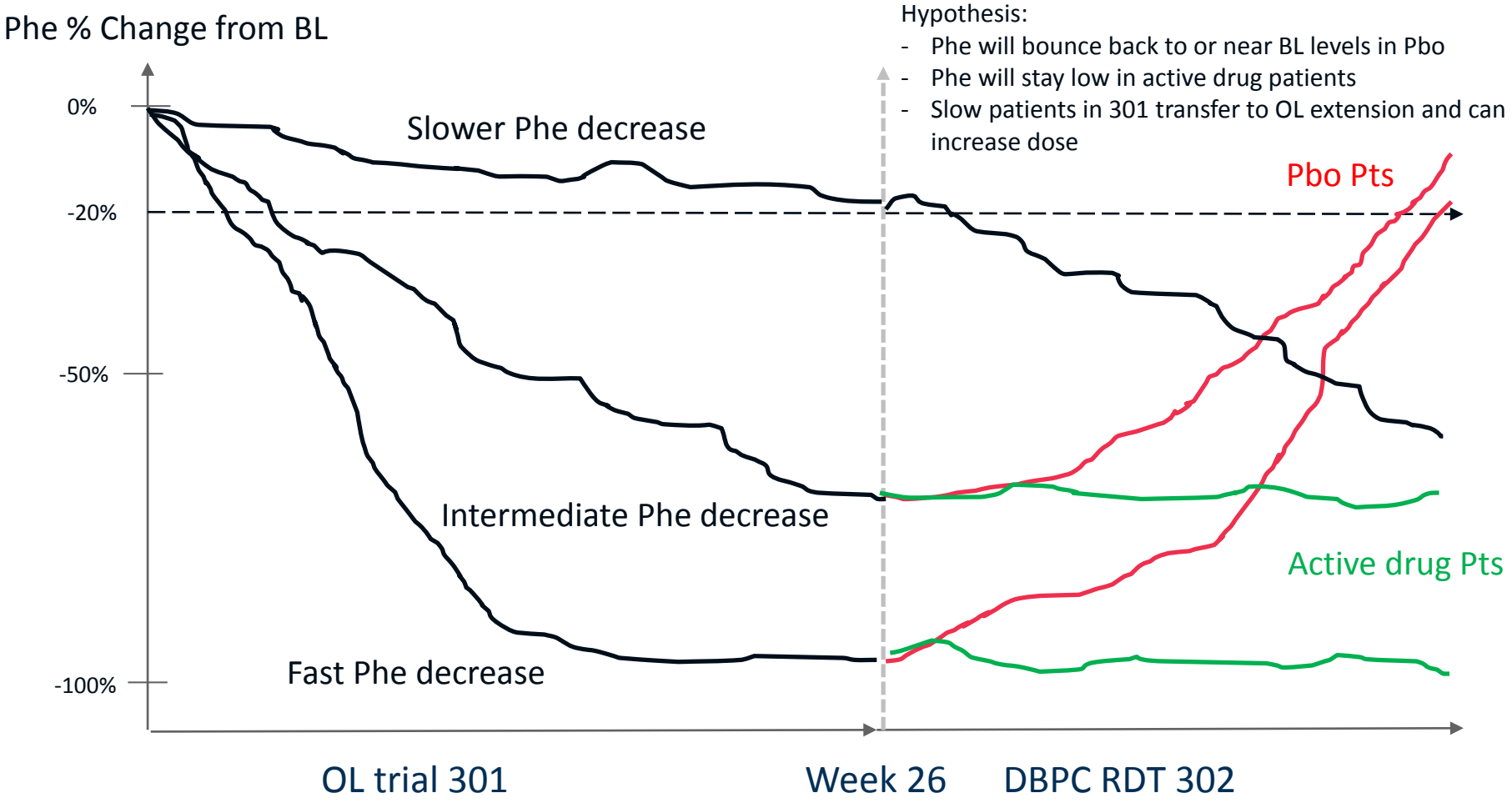
Phe eligibility criteria to enter RDT/302:

- Some patients had a stronger initial immune response and less Phe reduction by week 26
- A minimum Phe reduction requirement was introduced to eliminate slow responders from 302 study
- Therefore, patients with slow initial Phe reduction from 302 are being randomized to discontinuation portion
    - These patients are escalated to 40mg or 60mg in extension study 303 for further Phe reduction

Modified safety measures:

- Premedication during induction/titration phase

Enrichment Strategy Achieves 60% mean Phe Reduction at start of RDT study 165-302



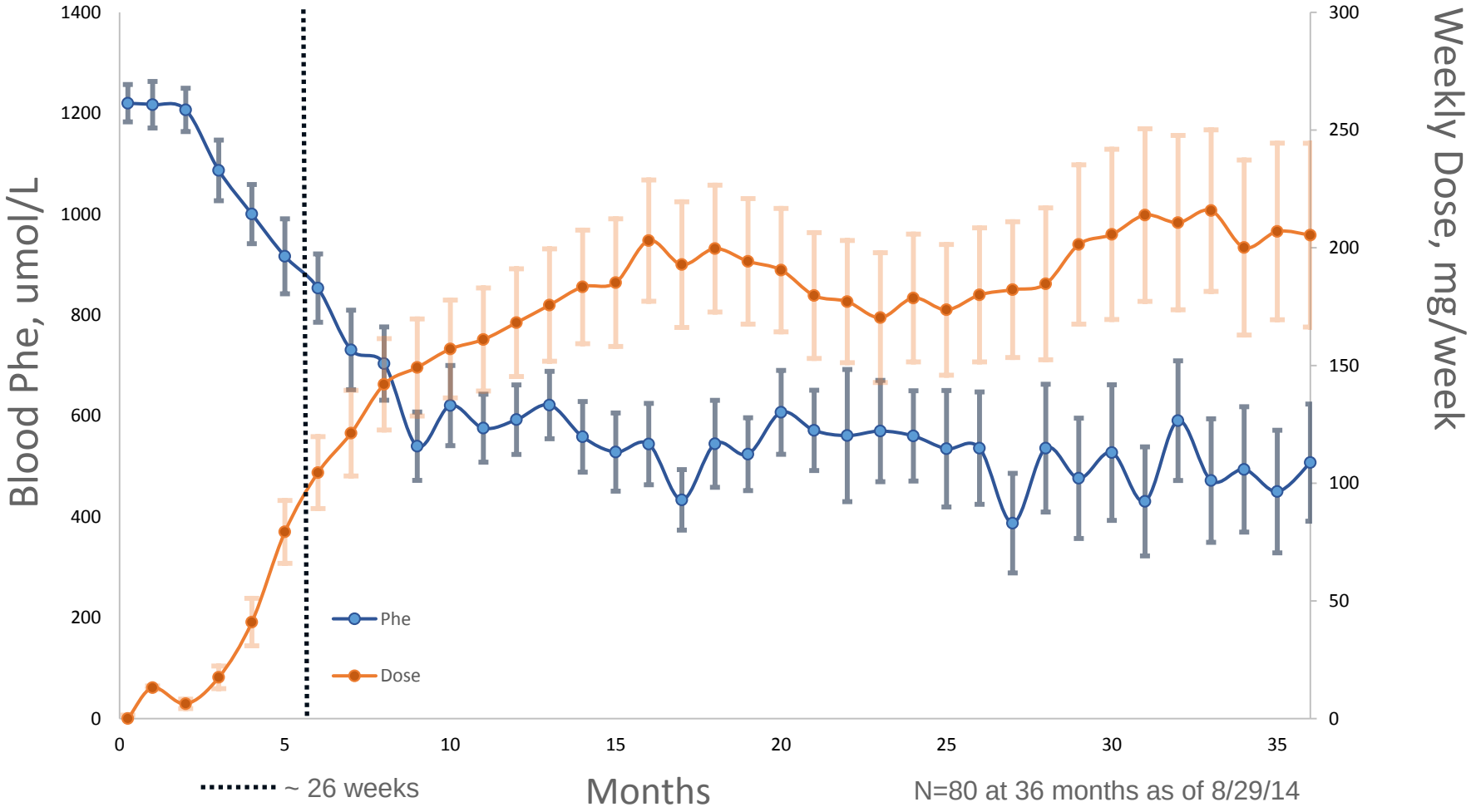
Patients with slow Phe decrease are eliminated from RDT

Summary on Blood Phe in 165-301 and 165-302 Part 1

Preliminary data as of 10/31/2014

	BMN 165 Dose Group	165-301 Baseline Blood Phe, umol/L	Mean change from 165-301 baseline to mean of last two blood Phe, umol/L	Mean percent change in blood Phe from 165-301 baseline
Subjects who have reached target dose with ≥20% Phe reduction from 165-301 baseline	20 mg (n=25)	1323	-753	**-58%**
	40 mg (n=29)	1195	-729	**-60%**

BMN 165 Phase 2: Mean Blood Phe and Dose Over Time
Phe Reduction Maintained out to 36 months



Program Changes – Conclusions so far…

- Elimination of slow Phe responders achieves robust mean Phe reduction of ~60% when entering RDT study
  - Increases chance of success for the pivotal RDT experiment
  - Patients not achieving 20% Phe reduction during 301 can achieve more Phe reduction during OL extension (with or w/o higher doses)

- Preliminary experience with modified premeds is positive

- Pivotal data expected 1Q16

Where are we with Regulators?

- FDA supports changes to program
- Based on comprehensive Meta-Analysis data, awareness of unmet medical need, importance of Phe reduction *in adults* and neurocognitive manifestations in adult PKU patients is strengthened
- A favorable outcome on a prospectively-specified analyses of inattention (recognizing the limitations of the study power) in patients with baseline problems with attention could be strongly supportive of a *FULL* approval



Cary Harding, M.D.
Professor of Molecular and
Medical Genetics and Pediatrics
Oregon Health & Science University

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rAvPAL-PEG Update

Cary O. Harding, MD
Professor, Molecular and Medical Genetics
Oregon Health & Science University
Portland, OR

Objectives

- Describe the need for novel therapy in PKU
- Review the goals of successful treatment
- Present the efficacy of treatment with rAvPAL-PEG
- Review the nature and management of hypersensitivity reactions following rAvPAL-PEG
- Discuss the risks vs. benefits of rAvPAL-PEG
- Conclusions

The need for novel therapy

- Comparison of well-treated PKU patients with unaffected siblings
  - IQ 8-10 points lower on average in PKU
  - Higher incidence of learning disabilities
    - Visuospatial skills
    - Attention deficit/hyperactivity

Azen, C.G., et al., *Intellectual development in 12-year-old children treated for phenylketonuria.* Amer. J. Dis. Child., 1991. **145**(1): p. 35-39.

The need for novel therapy

- Nonadherence to complicated, unpalatable diet
  - 75% of adolescents with blood Phe above recommended levels

Walter, J.H. and F.J. White, *Blood phenylalanine control in adolescents with phenylketonuria.* Int J Adolesc Med Health, 2004. **16**(1): p. 41-5.

The need for novel therapy

- Maternal PKU syndrome
  - Fetal teratogenesis
  - Microcephaly
  - Developmental delay
  - Congenital heart disease

Platt, L.D., et al., *The international study of pregnancy outcome in women with maternal phenylketonuria: report of a 12-year study.* Am J Obstet Gynecol, 2000. **182**(2): p. 326-33.

The need for novel therapy

- Adult onset white matter degeneration
  - Spasticity
  - Ataxia
  - Seizures

Thompson, A.J., et al., *Neurological deterioration in young adults with phenylketonuria.* Lancet, 1990. **336**: p. 602-605.

The need for novel therapy

- Impaired executive functioning and mood disorders
  - Inattention
  - Slow processing speeds
  - Difficulty executing complex tasks
  - Anxiety

VanZutphen, K.H., et al., *Executive functioning in children and adolescents with phenylketonuria.* Clin Genet, 2007. **72**(1): p. 13-8.

Christ, S., et al., *Executive function in early-treated phenylketonuria: Profile and underlying mechanisms.* Molecular Genetics and Metabolism, 2010. **99**(Supplement 2010): p. S22-S32

The key question

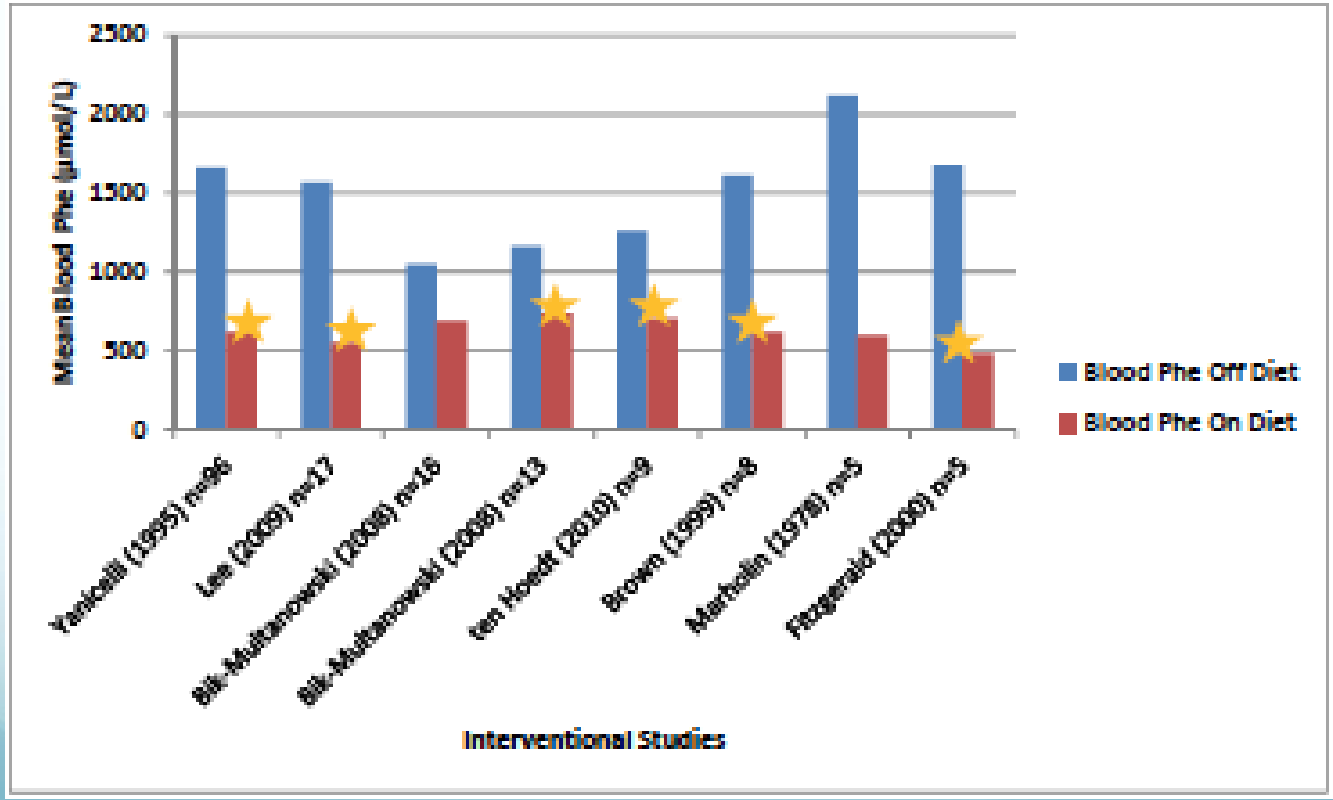
Will lowering blood Phe in adults improve neuropsychiatric symptoms?

Or

Are these symptoms due to irreversible brain damage suffered after long standing hyperphenylalaninemia?

Meta-analysis of Neuropsychiatric Outcomes in Adults with PKU

Figure 2. Blood Phe Levels Off-Diet and On-Diet for Interventional Studies in Adults with PKU and Psychiatric Symptoms



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SYSTEMATIC REVIEW | Genetics inMedicine

Open

Recommendations for the nutrition management of phenylalanine hydroxylase deficiency

Rani H. Singh, PhD, RD[1], Fran Rohr, MS, RD[2], Dianne Frazier, PhD, MPH[3], Amy Cunningham, MS, RD[4], Shideh Mofidi, MS, RD[5], Beth Ogata, MS, RD[6], Patricia L. Splett, PhD, MPH[7], Kathryn Moseley, MS, RD[8], Kathleen Huntington, MS, RD[9], Phyllis B. Acosta, DrPH, RD[10], Jerry Vockley, MD, PhD[11,12] and Sandra C. Van Calcar, PhD, RD[13]

Genetics inMedicine | ACMG PRACTICE GUIDELINES

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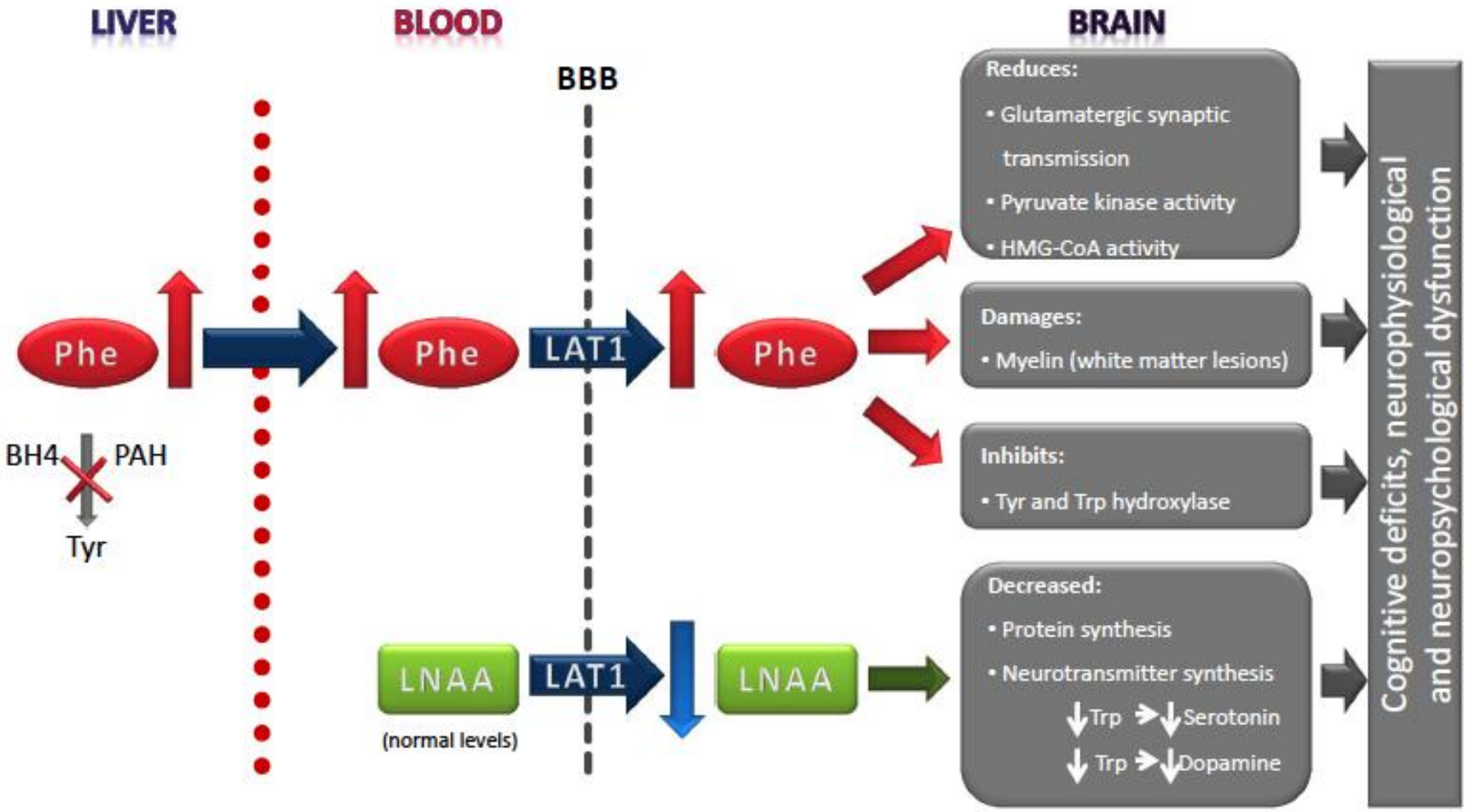
Phenylalanine hydroxylase deficiency: diagnosis and management guideline

Jerry Vockley, MD, PhD[1,2], Hans C. Andersson, MD[3], Kevin M. Antshel, PhD[4], Nancy E. Braverman, MD[5], Barbara K. Burton, MD[6], Dianne M. Frazier, PhD, MPH[7], John Mitchell, MD[5], Wendy E. Smith, MD[8], Barry H. Thompson, MD[9] and Susan A. Berry, MD[10]; For the American College of Medical Genetics and Genomics Therapeutic Committee

Genetics in Medicine vol.16, issue 2, February, 2014

Treatment recommendations

- Reaffirmed treatment for life
- Altered recommendations for blood Phe target
  - Blood Phe = 120-360 µM
  - Infants and children
  - Adults
  - Pregnancy
- Encouraged research into novel therapies that don't solely rely upon dietary intervention

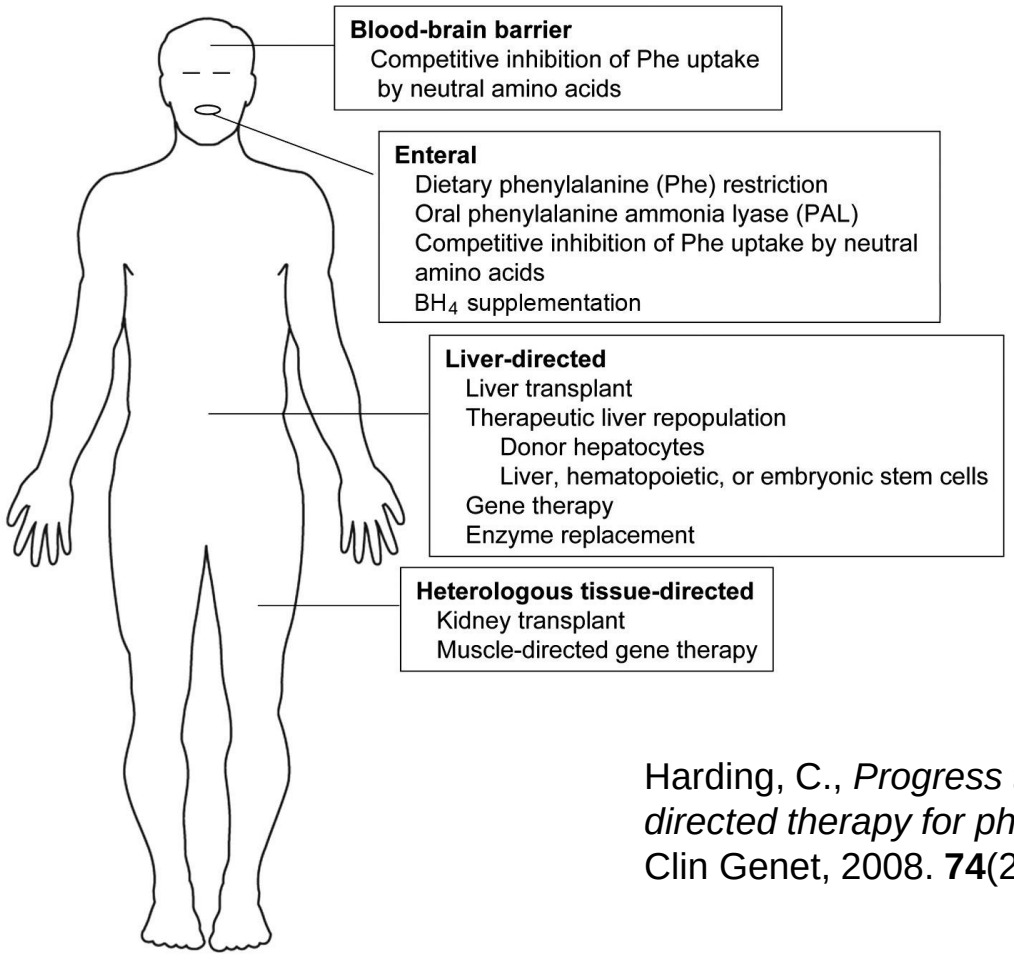


Feillet et al. 2010

What is needed to cure PKU?

Decrease brain phenylalanine

Potential therapies for PKU



Harding, C., *Progress toward cell-directed therapy for phenylketonuria.* Clin Genet, 2008. **74**(2): p. 97-104.

My perspectives on the treatment goal

- Impossible over the long term in adults using solely dietary therapy
- Emerging long term adverse effects of dietary therapy
  - Potential for micronutrient deficiency
  - Increased urinary acid excretion
  - Osteopenia
- Long term consequences of mildly elevated Phe
- Why not try to achieve normal Phe (60-120 µM)?

rAvPAL-PEG is the first therapy that has the potential to lower blood/brain Phe while allowing consumption of a healthy, unrestricted diet.

rAvPAL-PEG Efficacy

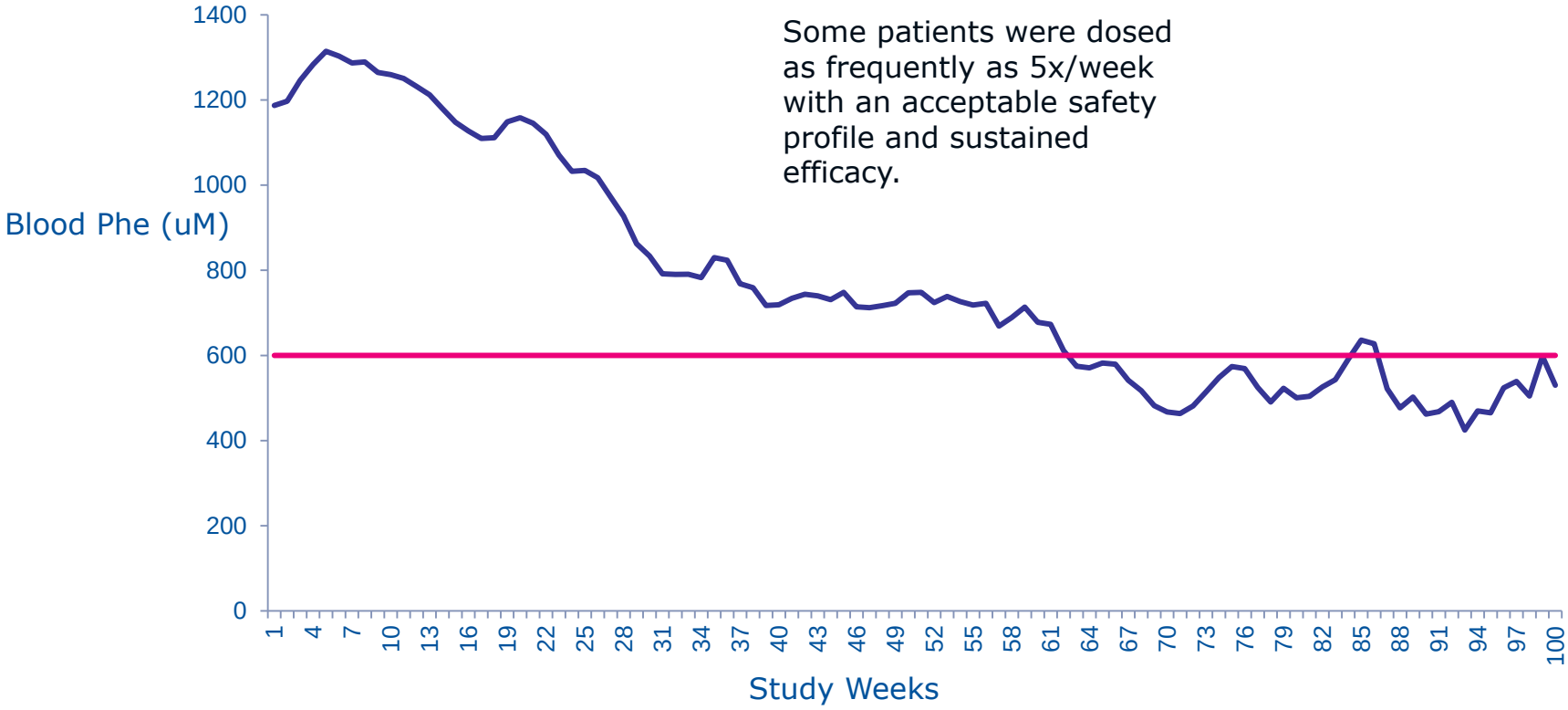
- Most (> 95%) subjects will reach therapeutic efficacy eventually
  - Dose dependent
  - Time dependent
  - In a few subjects, hypersensitivity reactions will preclude continuing PEG-PAL

- Effective dose appears to be determined by:
  - Antibody response (predominantly anti-PAL IgG)
  - Body mass
  - More study needed.

Weekly Induction Regimen Followed by Titration and Maintenance Results in Long Term Phe Reduction

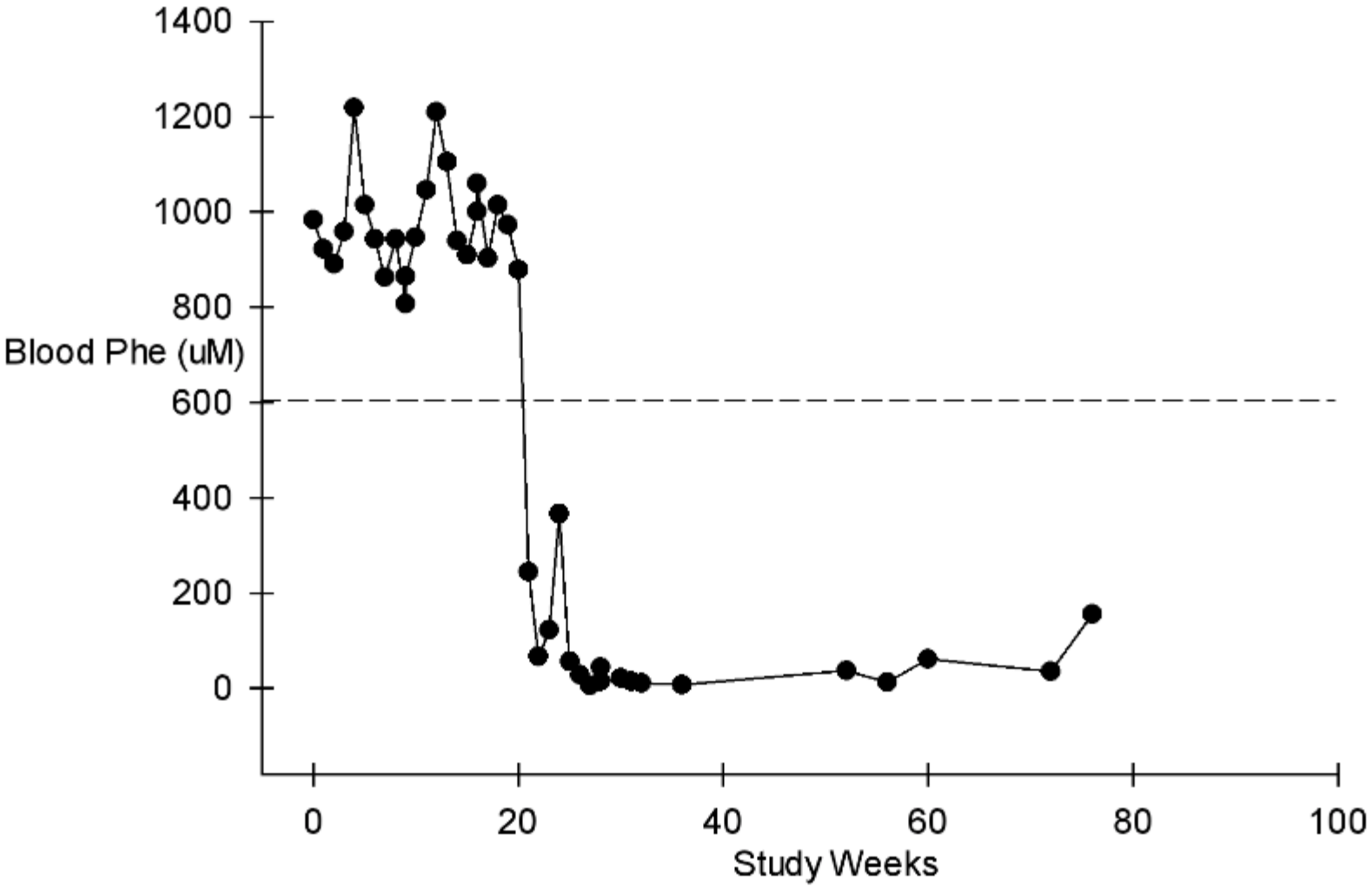
0.001-0.1 mg/kg weekly [PAL-002]

Variable dosing schedule. Median dose required for efficacy = 1mg/kg [PAL-003]



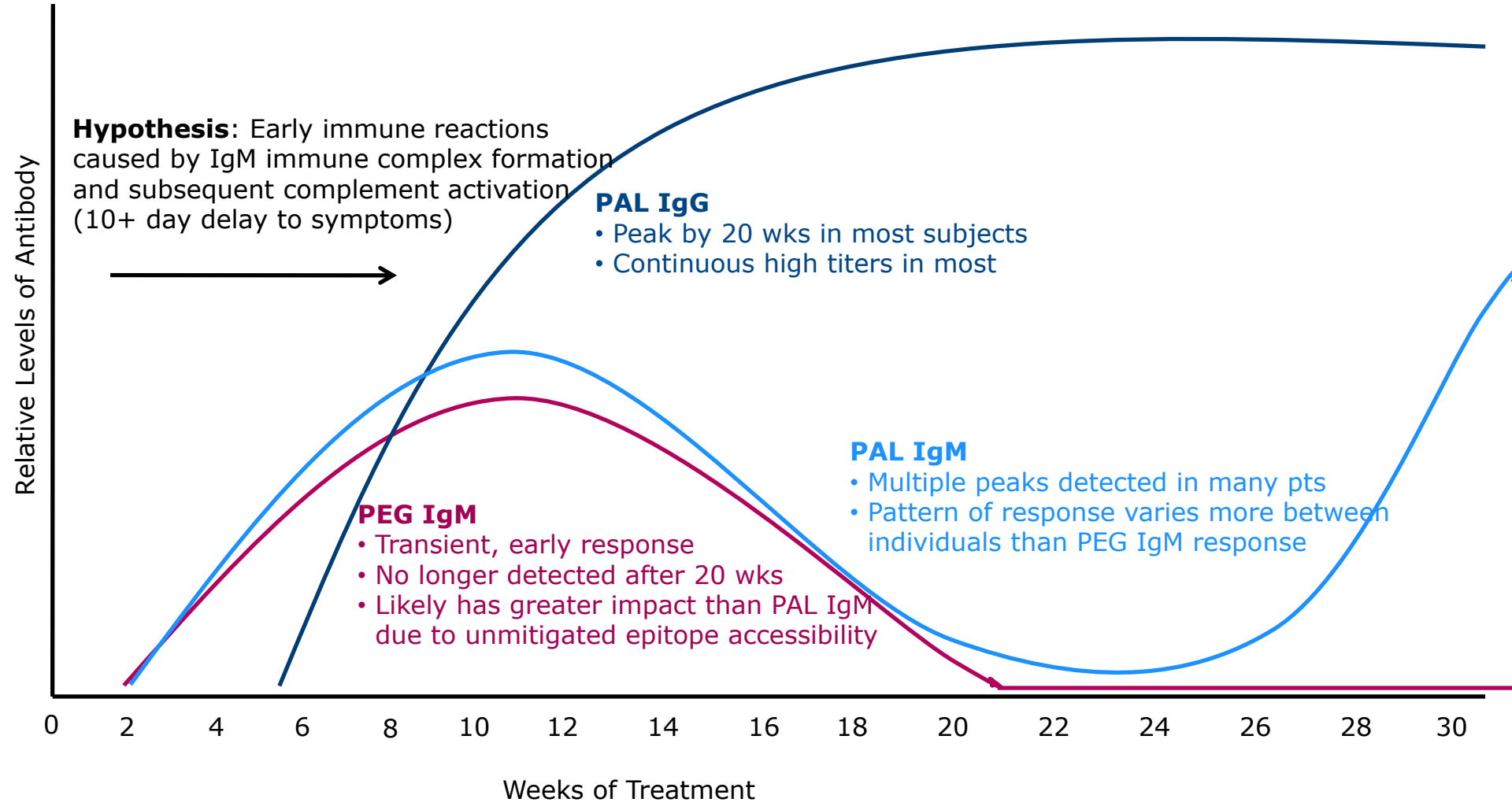
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In ~20% of Patients Continuing Therapy Reduction is Dramatic!



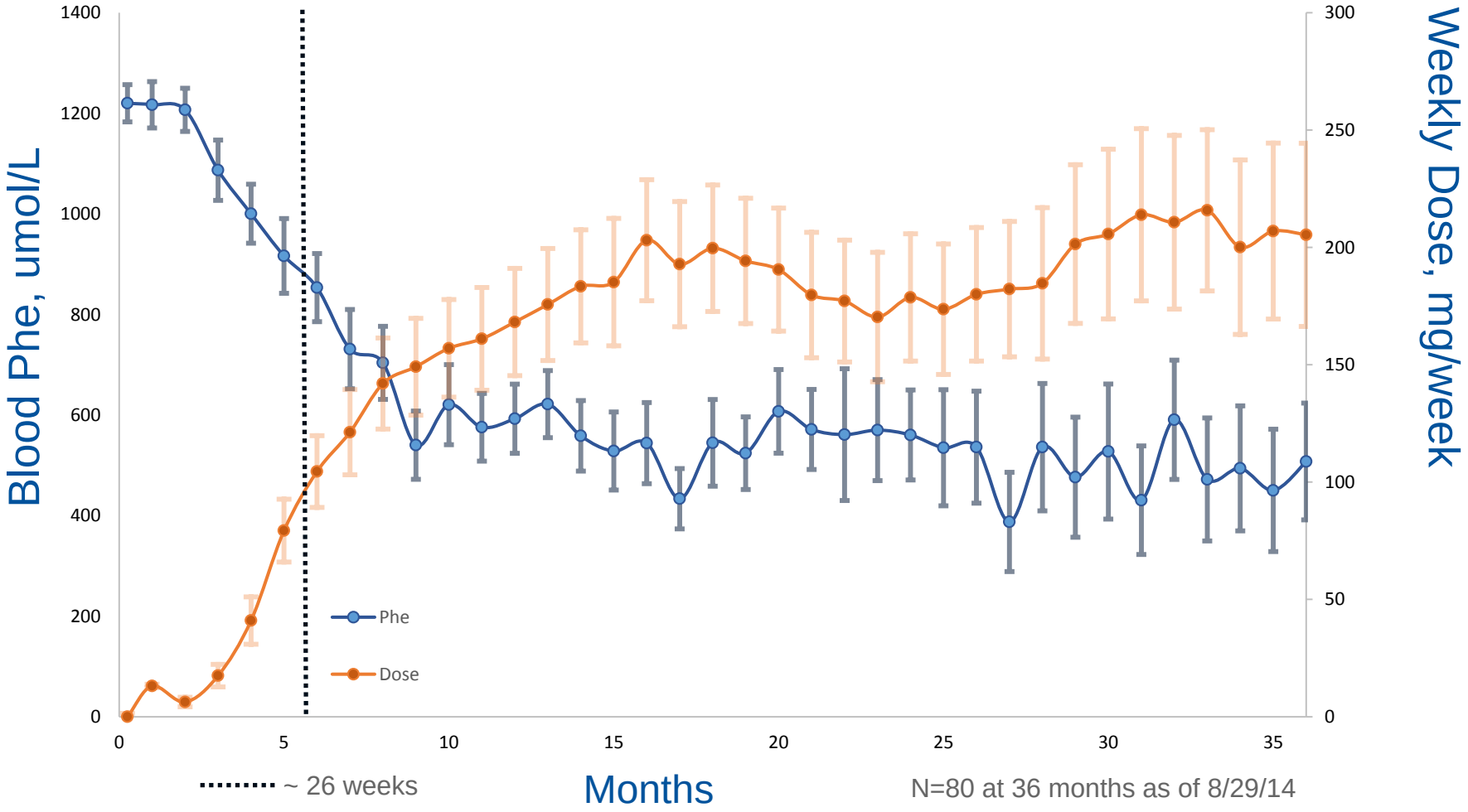
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For Optimal Safety: Keep Doses Low When IgM is Highest
For Optimal Long Term Efficacy: Titrate Up as PAL IgG Rises
Optimal Timing of Induction and Titration: Under Investigation



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BMN 165 Phase 2: Mean Blood Phe and Dose Over Time Phe Reduction Maintained out to 36 months



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Hypersensitivity reaction

- 50% of subjects in Phase 3 BMN-301 study have experienced hypersensitivity reactions
  - Injection site erythema and itching
  - More diffuse rash
  - Arthralgias
- Greatest risk during titration (6-20 weeks)
  - Peak anti-PEG IgM response
  - Increasing from 10 to 20 mg or 20 to 40 mg per day
  - Peak antigen/antibody complex prevalence
    - Inflammatory reaction
    - Complement fixation
    - Not IgE antibody mediated

Hypersensitivity

- Injection site reactions





Hypersensitivity











Management of hypersensitivity reactions

- Prevention (pretreatment)
  - Daily H1 antihistamine
  - Daily H2 antihistamine
  - Daily non-steroidal anti-inflammatory (NSAID)
  - Epipen available during induction/titration
- Treatment if reaction occurs
  - Dose reduction to last asymptomatic dose
  - Oral or IV steroid for severe reaction
  - Rechallenge with higher dose 4-6 weeks later when IgM will have decreased.
- Hypersensitivity reactions are generally transient and most patients can continue treatment

Risk/benefit analysis

- Risks
  - Hypersensitivity reactions are manageable
  - No longer term adverse effects yet known
    - Several subjects nearing 4 years of treatment
- Benefits
  - Clinically significant reduction in blood Phe in the majority of subjects
  - Neuropsychiatric benefits need to be formally proven, but many subjects report improved mood, less anxiety, improved concentration with lower blood Phe

Neuropsychiatric benefits of lower blood Phe

- Meta-analysis strongly suggests benefits from lower blood Phe using dietary therapy
- BMN 165-302 study is critical for characterizing the neuropsychiatric benefits of lower blood Phe
  - Study measures
    - POMS – mood disorders including anxiety
    - Observer rated inattention scale
  - Executive function (Cantab) to be tested in a sub-study currently under development
  - RDT will prove the short term (8 weeks) benefits
  - Extension study will prove the longer term benefits

Conclusions

- Novel therapies for PKU are needed.
- rAvPAL-PEG is the first therapy in clinical trials that has the potential to completely normalize blood Phe while consuming an unrestricted diet.
- Proof of neuropsychiatric benefits with lower Phe is paramount to the acceptance of novel therapies by the greater medical community.
- Long term benefits and risks will require further study.

Q&A



Craig McDonald, M.D.
Professor and Chair,
Department of Physical Medicine & Rehabilitation,
School of Medicine, UC Davis Health System

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Drisapersen: an overview of the clinical program in Duchenne muscular dystrophy

Craig McDonald, MD
Professor and Chair
Physical Medicine & Rehabilitation
Professor of Pediatrics

UCDAVIS
CHILDREN'S HOSPITAL

Neuromuscular Research Center

Discovering
Creates
Hope

Disclosures

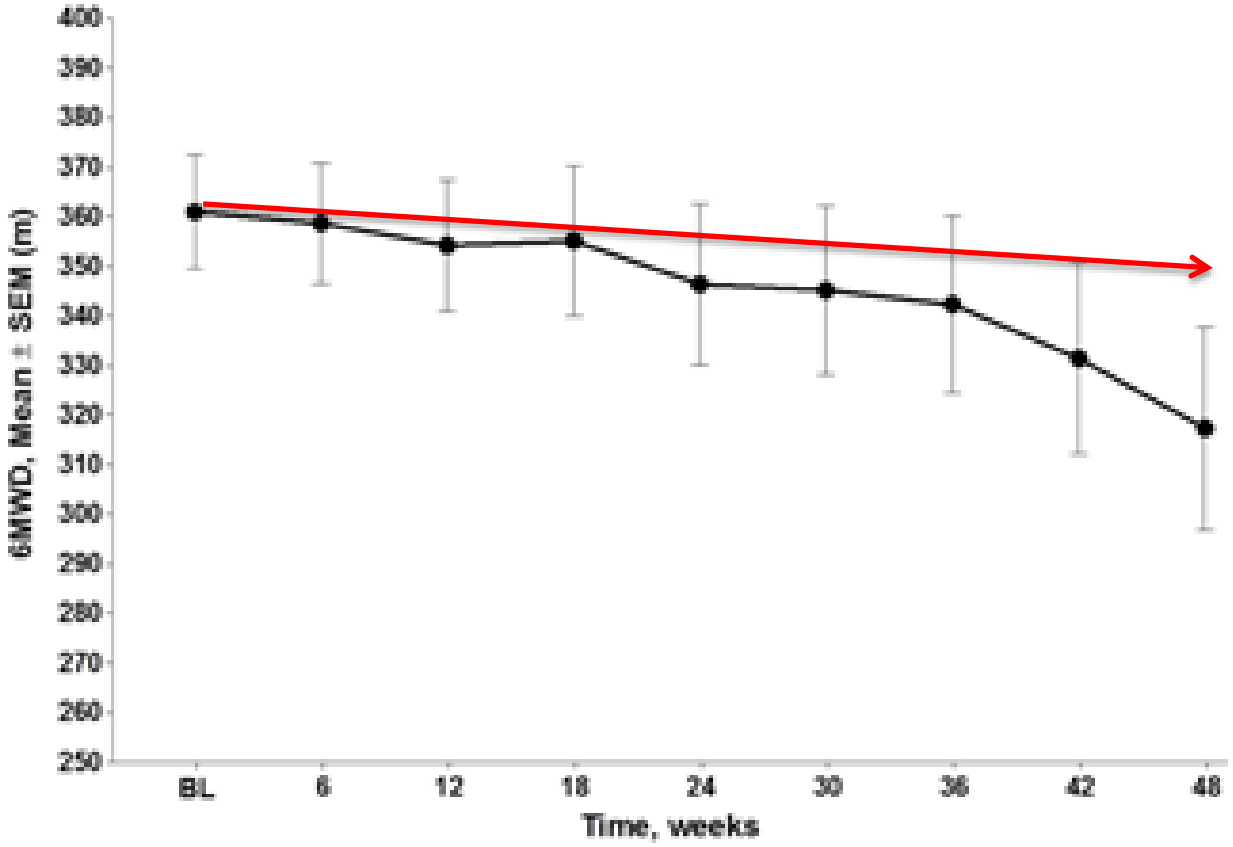
- Consulting work on Duchenne muscular dystrophy clinical trials for
  - PTC Therapeutics
  - Sarepta
  - Prosensa
  - Pfizer
  - Eli Lilly
  - Halo Therapeutics
  - Bristol Myers Squib
  - Novartis
  - Italfarmaco
  - Mitokyne
  - Cardero Therapeutics
- Site investigator for phase 3 trials for ataluren and eteplirsen
- Site investigator and study PI for DEMAND V study of drisapersen
- Site investigator for drisapersen extension trial

Introduction

- Duchenne muscular dystrophy (DMD) is a severely debilitating and ultimately fatal childhood disease
  - Affects 1 in 3500–5000 newborn boys[1,2]
  - Characterized by a progressive decrease in muscle function[3] leading to loss of ambulation, respiratory failure and cardiomyopathy
  - Caused by mutations in the dystrophin gene, resulting in disruption of the open-reading frame, dystrophin deficiency and muscle fibre degeneration[4]
- Exon skipping:
  - A therapeutic strategy for restoring partial functional dystrophin expression
  - Aims to convert the more severe DMD into a milder Becker muscular dystrophy (BMD) phenotype
- Drisapersen:
  - A 2'-*O*-methyl-phosphorothioate antisense oligonucleotide that induces skipping of exon 51 in the dystrophin pre-mRNA
  - Can be used to correct mutations occurring in approximately 13% of boys with DMD[5]

1. Ellis JA, *et al. Neuromuscul Disord* 2013;23:682–9. **2**. Mendell JR, *et al. Muscle & Nerve* 2013;48:21–6. **3**. Emery AE. *Duchenne Muscular Dystrophy (3rd ed)*. Oxford University Press; Oxford, UK: 2003. **4**. Aartsma-Rus A, *et al. Muscle & Nerve* 2006;34:135–44. **5**. Hammond SM, Wood MJ. *Curr Opin Mol Ther* 2010;12:478–86.

Responsiveness of 6MWD to dystrophin restoration



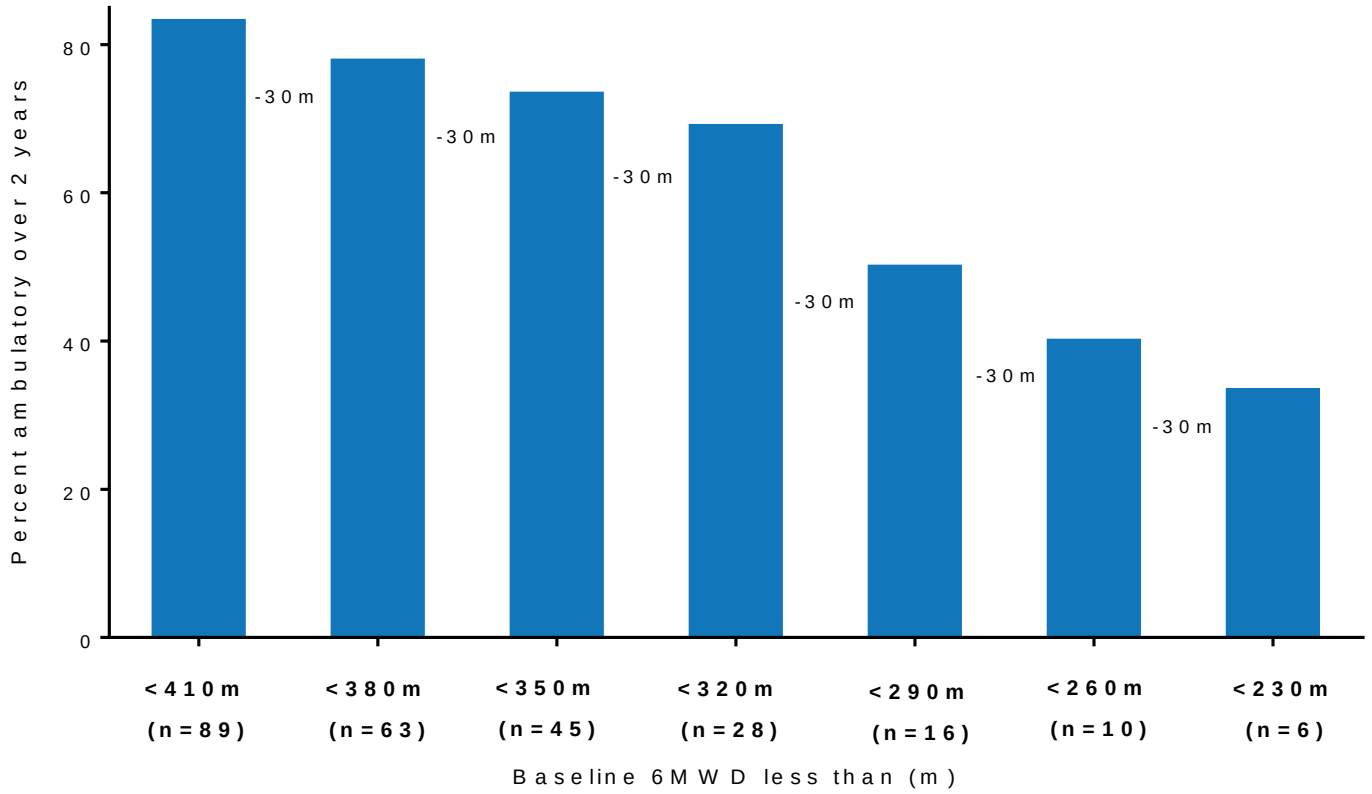
Δ -14 meters

Δ - 44.1 meters

Minimal clinically important difference (MCID) in 6MWD in DMD has been calculated to be 30 meters (McDonald *et al 2013)*

MCID definition	MCID for 6MWD in DMD	Reference
a. Baseline SD · √(1 – r)	28.5 m	McDonald 2013; Wyrwich 1999
b. Baseline SD/3	31.7 m	McDonald 2013; Yost 2005

Decline in 6MWD predicts loss of ambulation over 2 years



For every 30 m incremental decrease in baseline 6MWD, the percentage of patients who remain ambulatory over the following 2 years decreases substantially

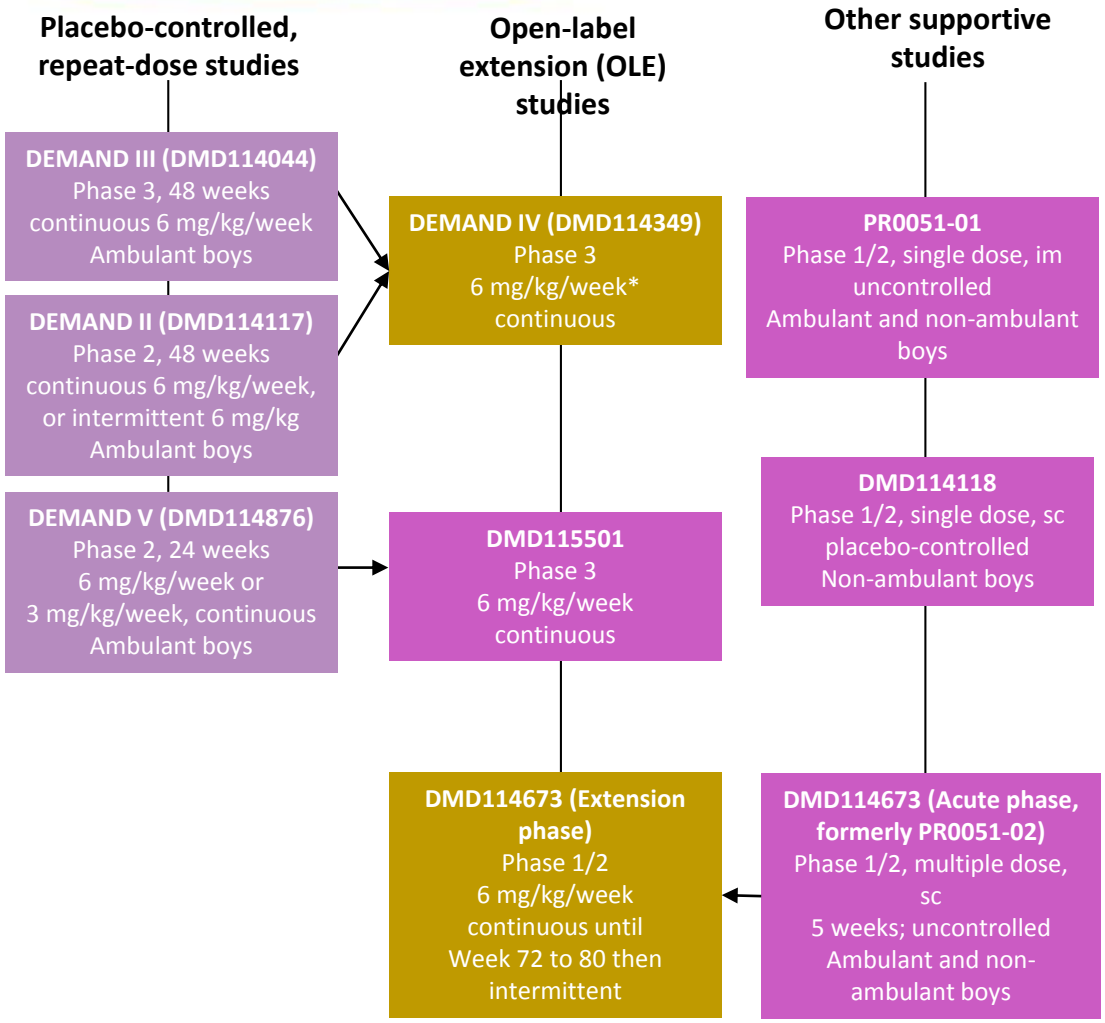
Adapted from Mazzone *et al. PLOS One*, 2013

Drisapersen Clinical Program

More than **300 patients** and over **450 patient treatment years** in global clinical program

Study	Phase	Study design	N	Status
CLIN-02 **DMD114673**	Phase I/II + Extension	Open label, repeat dose escalation (extension phase 6 mg/kg/wk intermittent);	12	Complete; extension ongoing
DEMAND I **DMD114118**	Phase I	Placebo-controlled, pharmacokinetics/safety; single dose	20	Complete
DEMAND II **DMD114117**	Phase II	Exploratory placebo-controlled, dose regimen comparison; ex-US, 24/48 wks	53	Complete
DEMAND III **DMD114044**	Phase III	Randomized, placebo-controlled, confirmatory study; global, 48 wks	186	Complete
DEMAND IV **DMD114349**	Phase II/III Extension	Open label, extension study for DEMAND II) & DEMAND III ; 96 wks	234	Closed
DEMAND V **DMD114876**	Phase II	Exploratory placebo-controlled, dose-comparison; US only, 24 wks	51	Complete
DMD115501	Phase II/III Extension	Open-label, extension study for US & Canadian subjects from DEMAND III, IV, V	72	Recruiting

Overview of the drisapersen clinical trial programme

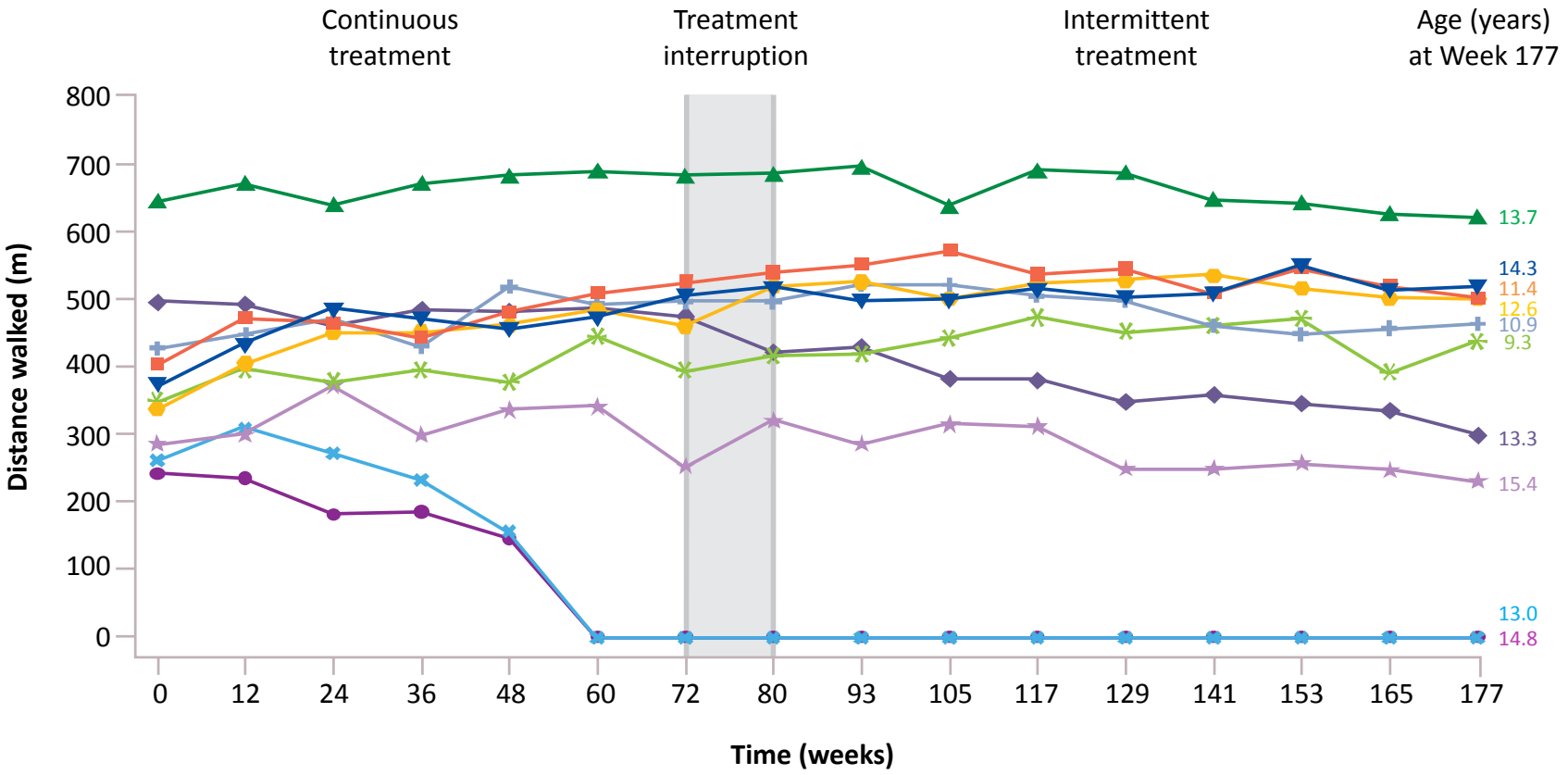


- Comprehensive clinical trial program to assess the safety and efficacy of drisapersen in DMD
  - Two Phase 2 and one Phase 3 randomized, placebo-controlled studies (total N=290)
  - Two open-label extension (OLE) studies (N=245)

*While continuous 6 mg/kg/week was the primary treatment arm for this study, some subjects moved to the intermittent dosing or natural history arms.
im, intramuscular; sc, subcutaneous.

- The totality of the clinical program efficacy data suggest:
  - benefit with drisapersen versus placebo in boys with less severe disease
  - clinically meaningful benefit after longer duration of drisapersen treatment in boys who are, on average, more severely affected

Open Label Extension study DMD114673: 6MWD



Mean age at 177: 12.9 yrs; **mean change from baseline 6MWD -25m, median +7.5m**

Data shown are for all subjects who completed the test at extension study baseline. One subject (subject 201) was non-ambulant at study entry and did not participate in any 6MWD tests while another subject (subject 103) was unable to complete the 6MWD test at extension study baseline. Data for both of these subjects are not shown here.

OLE study DMD114673: percent-predicted 6MWD

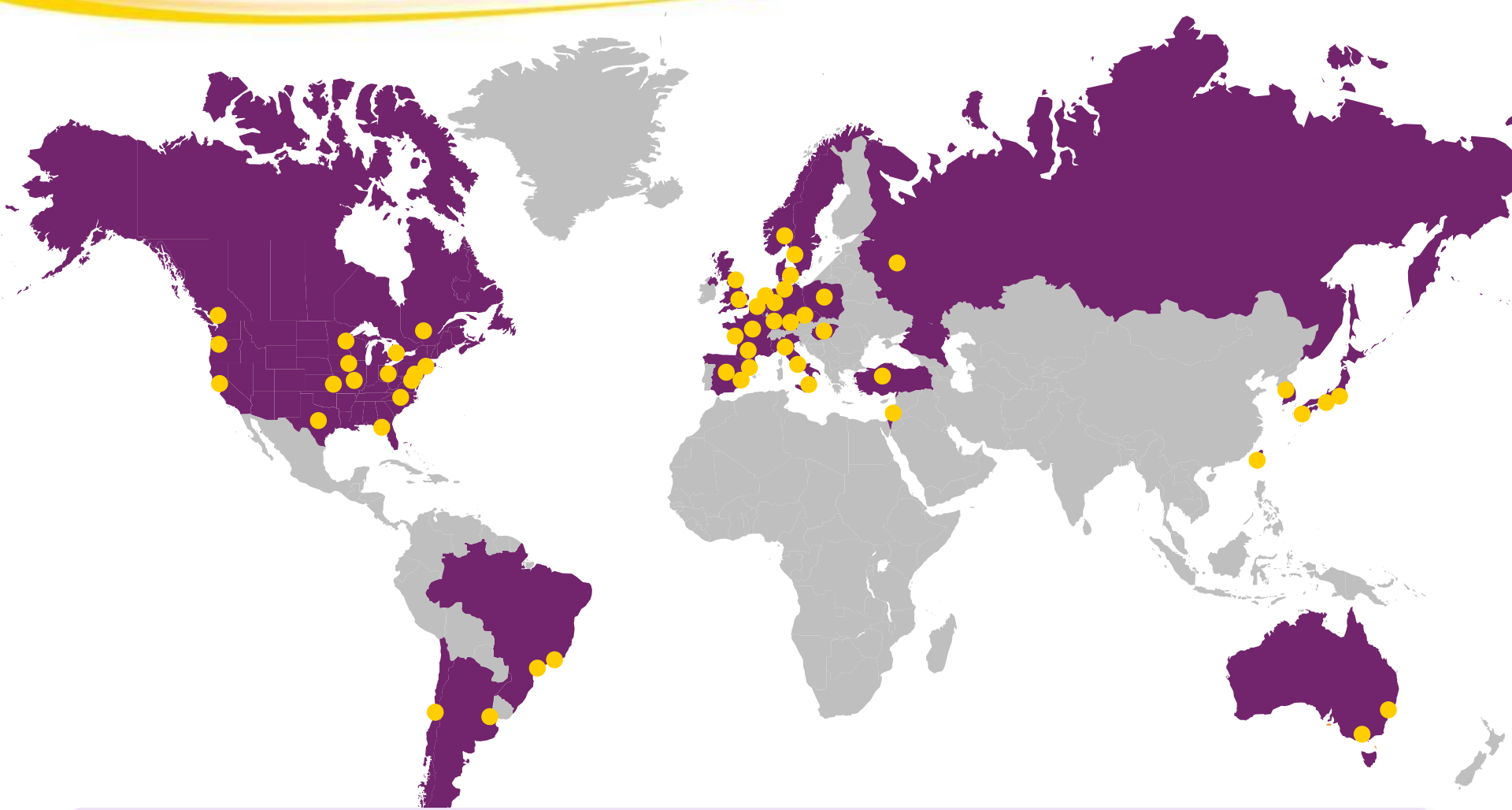
Subject*	Age (years)	OLE study baseline (% normal)	Week 177 (% normal)
101	9.6	59	79
102	6.7	69	78
104	9.1	104	96
105	8.4	56	78
106	9.0	42	0
107	10.9	37	0
202	6.5	75	74
205	11.1	45	35
206	5.1	69	74
207	9.3	82	46



Improvement from baseline in percent-predicted 6MWD was observed at Week 177 for 4/10 boys with available data

*Two subjects (103 and 201) unable to complete the 6MWD at OLE baseline are not shown.

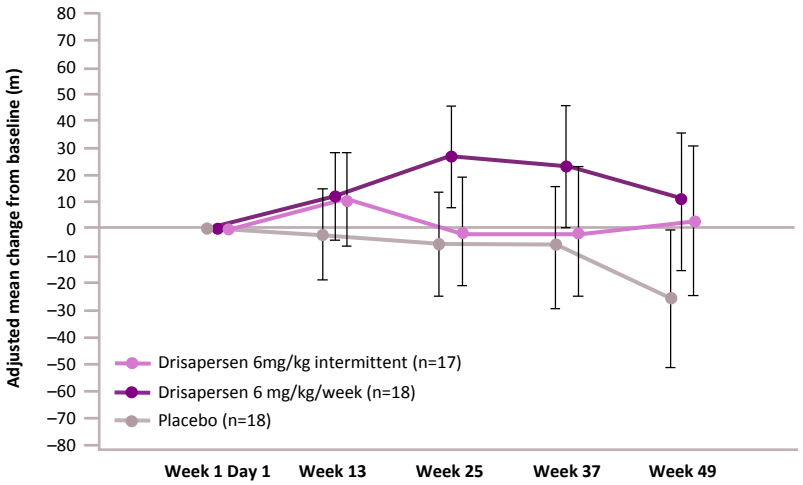
DMD114044 - Part of a Global Program



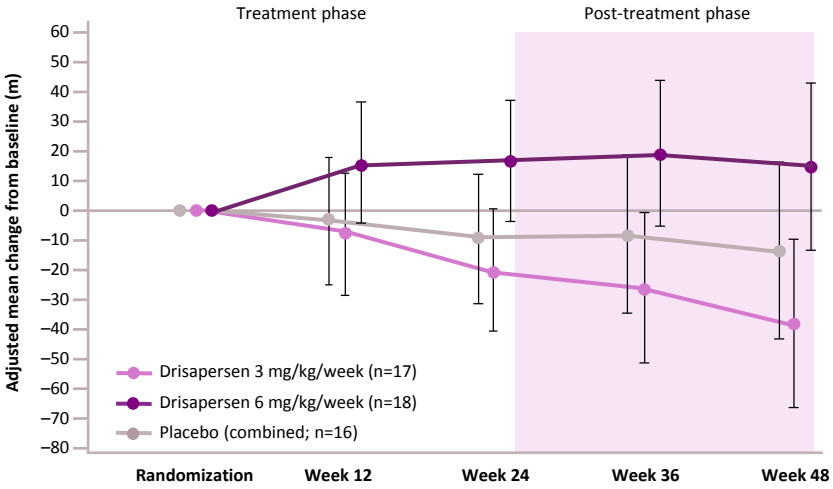
DMD114044 was conducted at 44 trial sites in 19 countries

Mean change from baseline in 6MWD in the Phase 2 and 3 studies

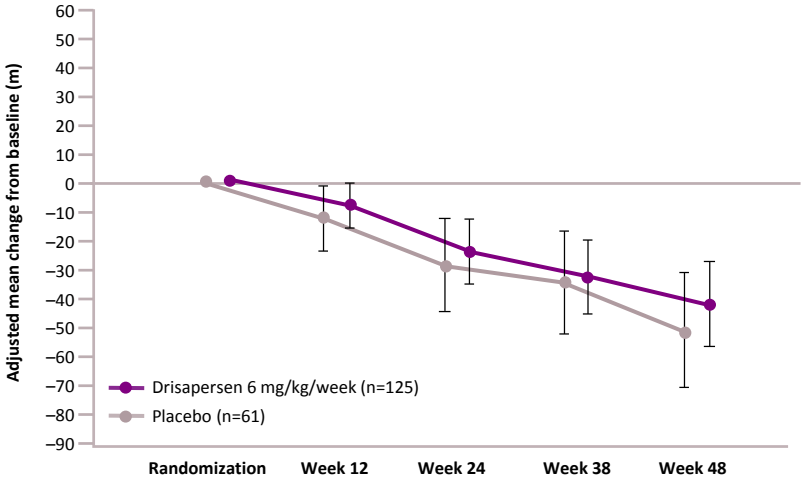
DMD114117



DMD114876



DMD114044



Difference in change from baseline in 6MWD for drisapersen 6 mg/kg/week versus placebo

DMD114117
Week 25: 35 m; p=0.014
Week 49: 36 m; p=0.051

DMD114876
Week 24: 27 m; p=0.069

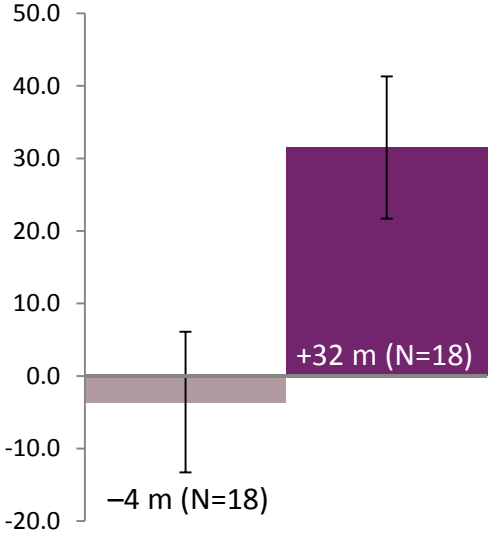
DMD114044
Week48: 10 m; p=0.415

6MWD pooled analysis of the Phase 2 studies*

A statistically significant treatment difference was observed for the change in 6MWD for the pooled analysis of the two Phase 2 studies

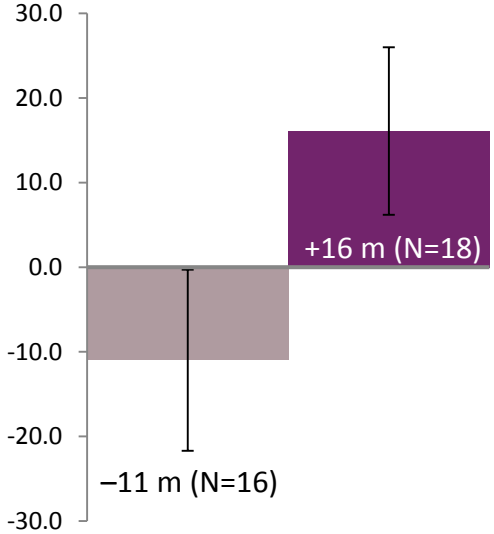
Placebo Drisapersen 6 mg/kg/week

Δ6MWD = +35 m
p=0.014



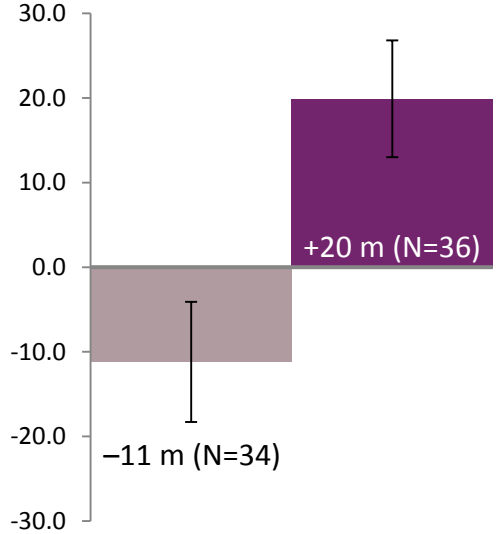
DMD114117
(Week 25 endpoint)

Δ6MWD = +27 m
p=0.069



DMD114876
(Week 24 endpoint)

Δ6MWD = +31 m
p=0.003

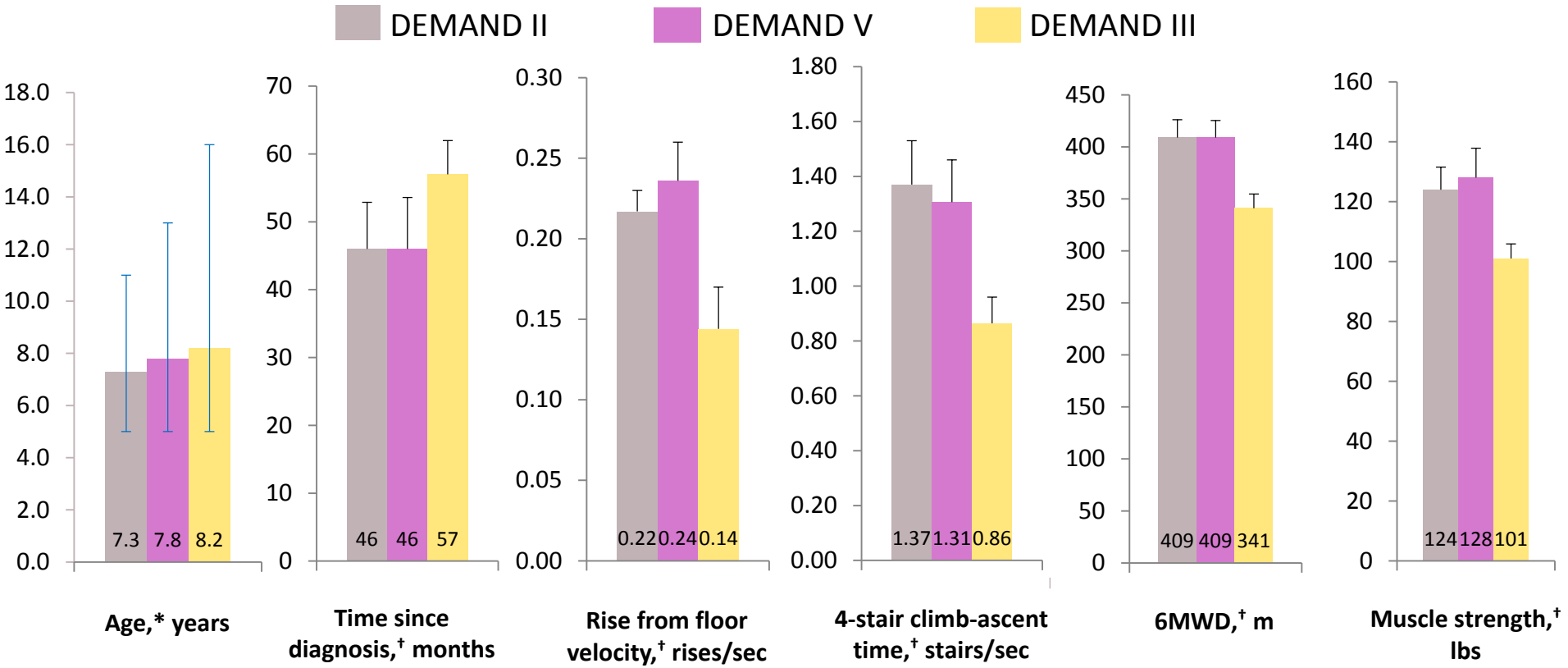


DMD114117 + DMD114876
(Week 24/25 post hoc analysis)

*The adjusted mean change from baseline in 6MWD for subjects enrolled in studies DMD114117 and DMD114876 was calculated.
Error bars show the standard error.

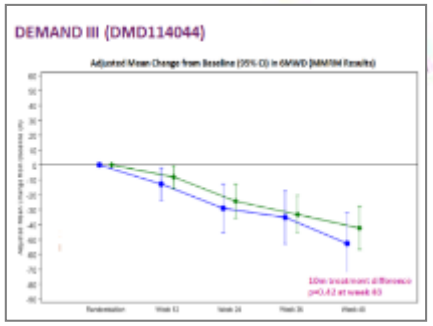
Study population baseline characteristics and timed function test results

Boys in DEMAND III were older and more advanced in disease



*Data shown are mean (range) for total study populations.
†Data shown are mean (95% CI) for total study populations.

DMD114044 – Primary Endpoint not met



Visit	Treatment	N	n	Unadjusted mean baseline value (sd)	Adjusted mean (se)	Treatment difference (m)	95% CI	P-value
All Subjects								
Week 48	Placebo	61	59	348 (92)	-53 (10)			
	Drisapersen	125	117	337 (96)	-42 (7)	+10	(-15,35)	0.415
≤ 7 years at baseline								
Week 48	Placebo	29	29	383 (67)	-25 (11)			
	Drisapersen	51	50	368 (65)	-4 (9)	+21	(-7,50)	0.131
> 7 years at baseline								
Week 48	Placebo	32	30	316 (101)	-83 (16)			
	Drisapersen	74	67	316 (107)	-76 (11)	+7	(-29,43)	0.703
Model includes terms for Treatment, Visit, Treatment by Visit, Study, Baseline 6MWD and Baseline 6MWD by Visit								

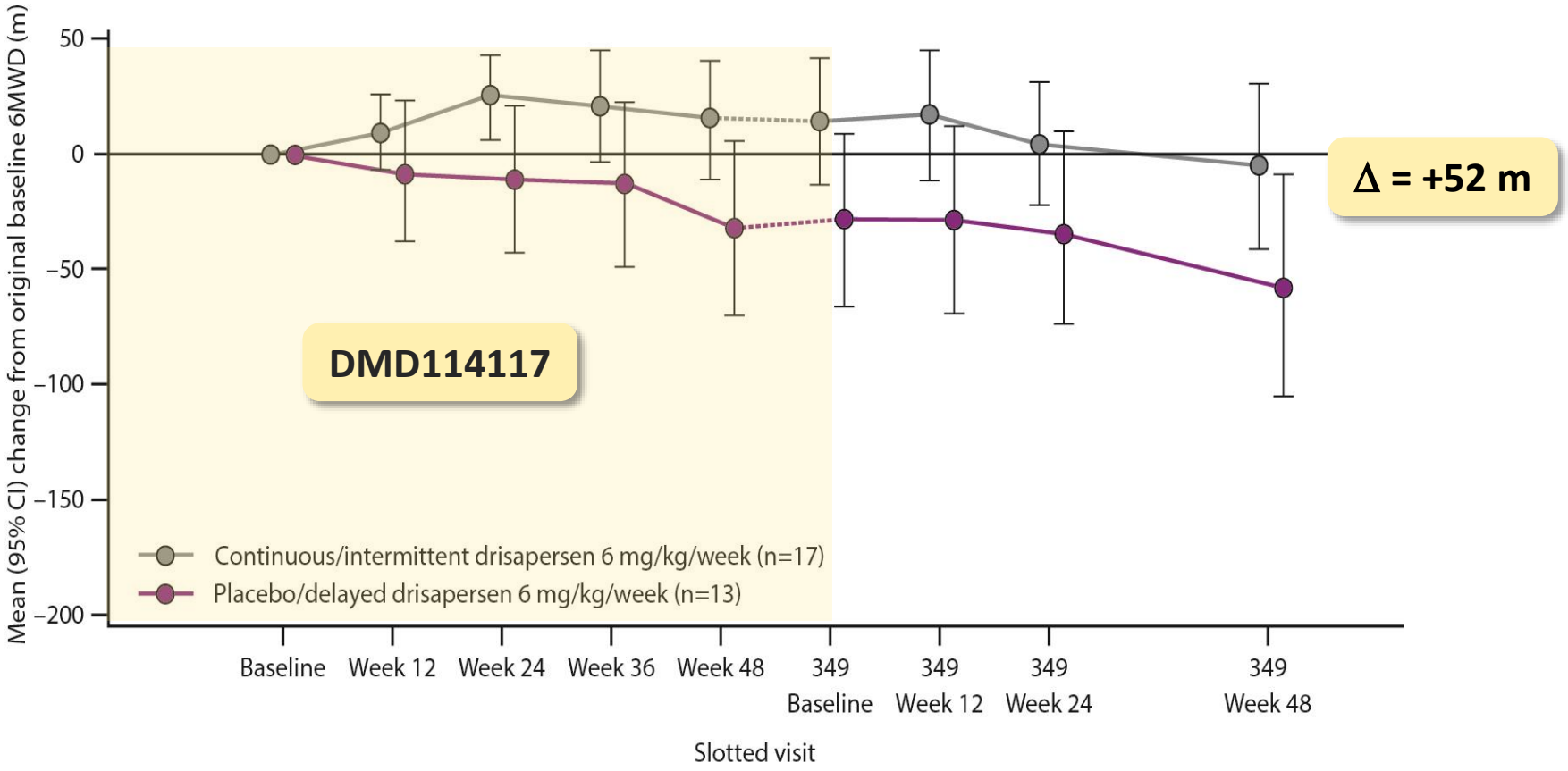
DMD114044 + DMD114117, Integrated Analysis

Visit	Treatment	N	n	Unadjusted mean baseline value (sd)	Adjusted mean (se)	Treatment difference (m)	95% CI	P-value
All Subjects								
Week 48	Placebo	79	77	361 (87)	-45 (9)			
	Drisapersen	143	135	349 (97)	-33 (7)	+13	(-9,34)	0.252
≤ 7 years at baseline								
Week 48	Placebo	42	42	391 (61)	-20 (9)			
	Drisapersen	62	61	376 (66)	+4 (8)	+24	(0,47)	0.048
> 7 years at baseline								
Week 48	Placebo	37	35	326 (99)	-68 (15)			
	Drisapersen	81	74	328 (111)	-61 (11)	+7	(-26,41)	0.670

Model includes terms for Treatment, Visit, Treatment by Visit, Study, Baseline 6MWD and Baseline 6MWD by Visit

98 week Extension: DMD114349 - By Feeder Study

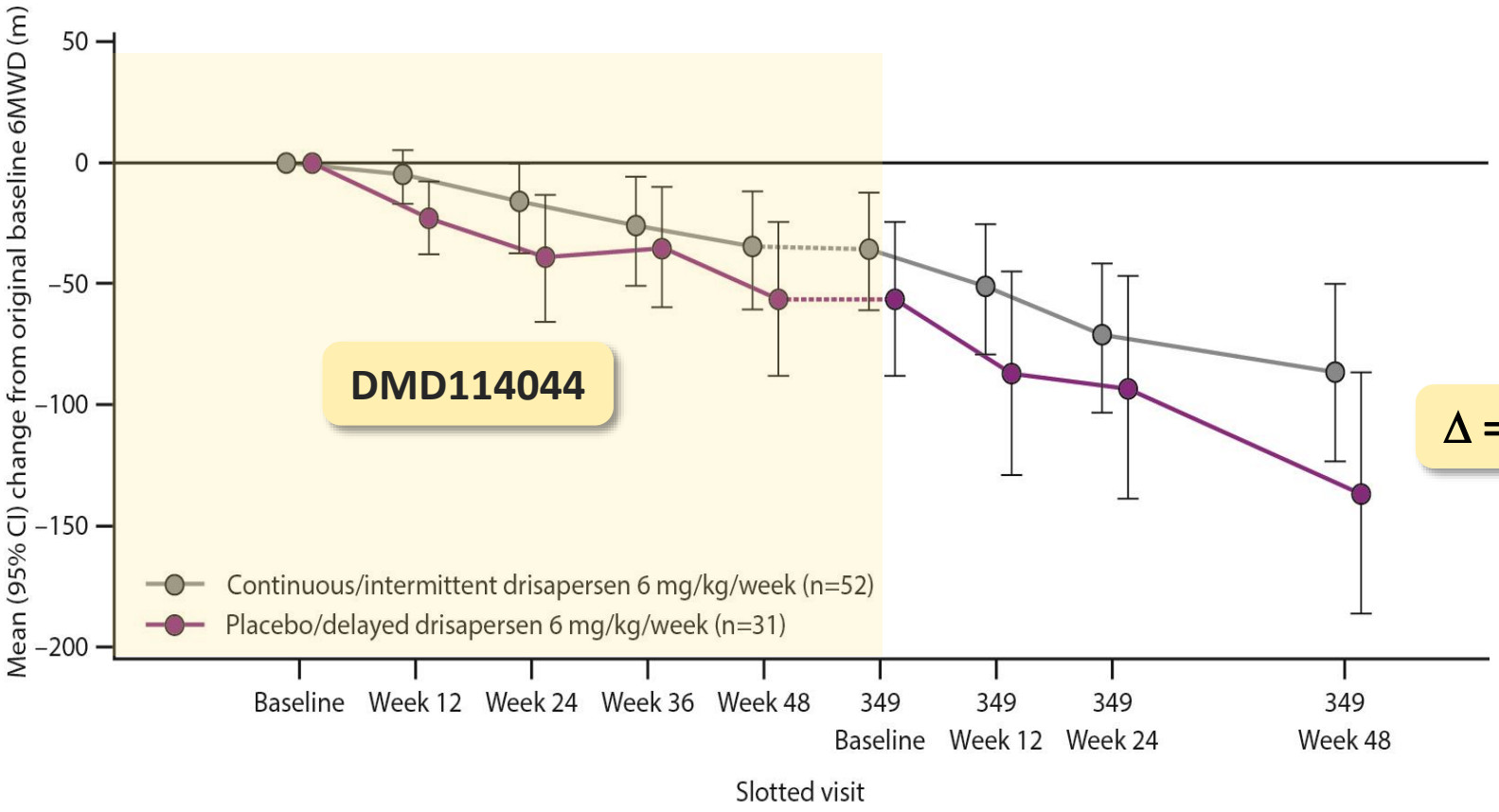
Earlier continuous treatment appears to show better effect on disease progression



Age at start of feeder study.

98 week Extension: DMD114349 - By Feeder Study

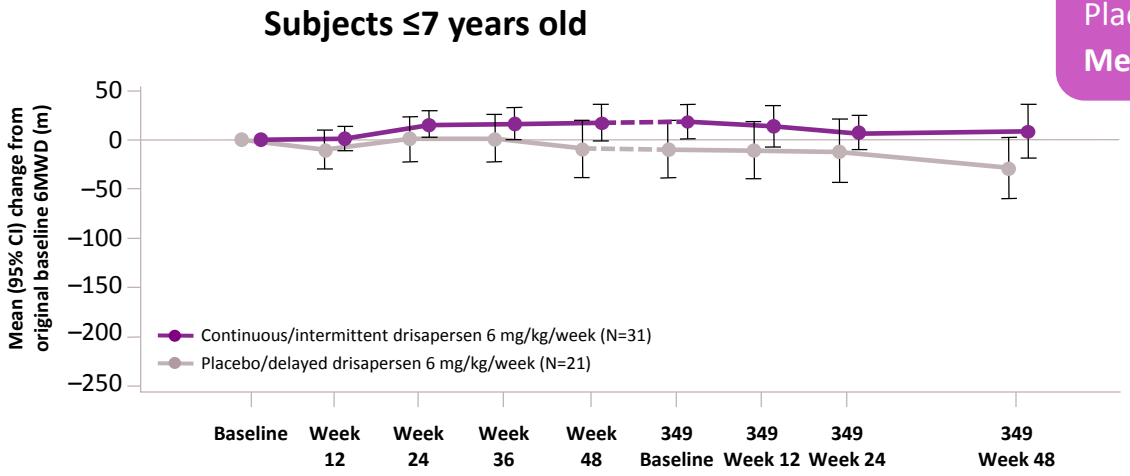
Longer treatment appears to show better effect on disease progression



Loss of ambulation imputed as 6MWD = 0

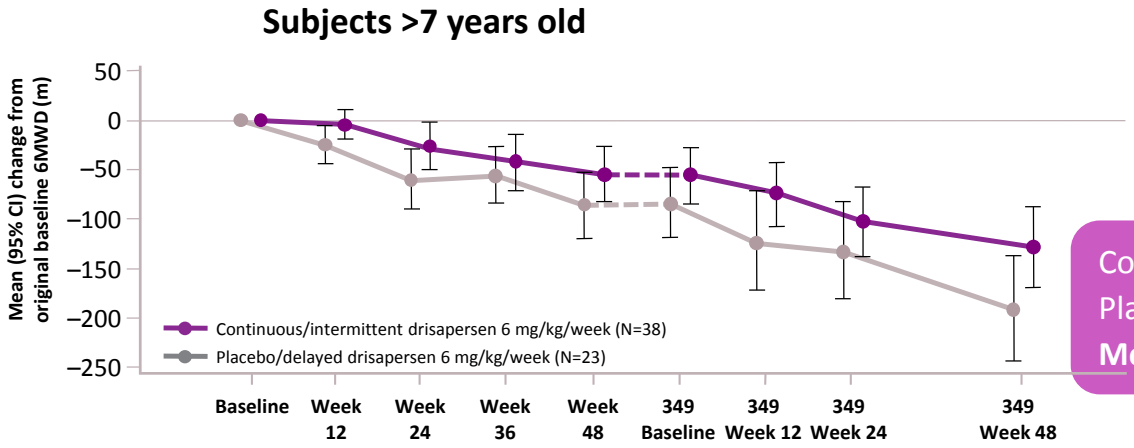
6MWD sub-group analysis by age group in the Open-Label extension study (DMD114349*)

Continuous/intermittent drisapersen: +8.4 m
Placebo/delayed drisapersen treatment: –28.7 m
Mean treatment difference: +37.1 m



Earlier treatment appears to show more favorable effect on disease progression

In more progressed patients, **longer treatment duration** may be required

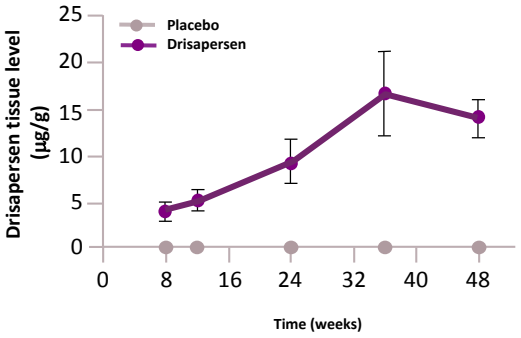


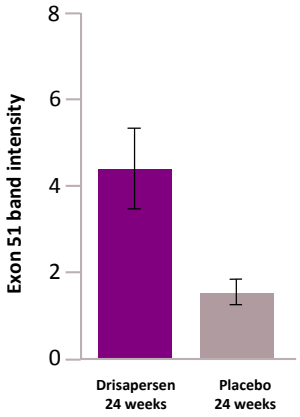
Continuous/intermittent drisapersen: –128.1 m
Placebo/delayed drisapersen treatment: –189.7 m
Mean treatment difference: +61.6 m

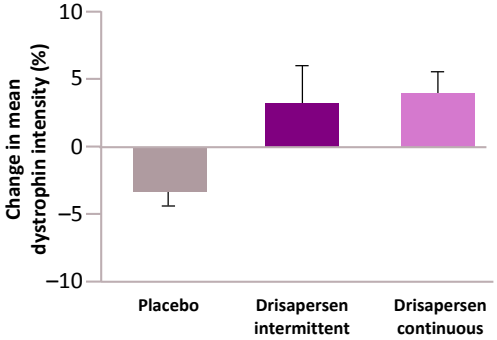
*Data presented are integrated data from 14 October 2013 (using the 6 June data cut).

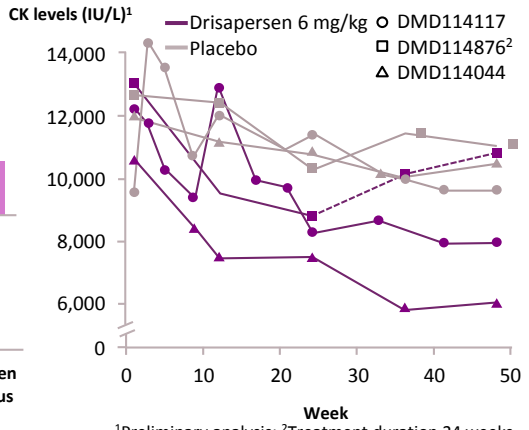
Drisapersen: effect on muscle

Leaky muscle fibres in DMD promote AON uptake → AONs enter nuclei, bind to exon 51 of DMD pre-mRNA, and induce skipping → Exon 51 skipping results in novel dystrophin production → Improved muscle physiology and structure



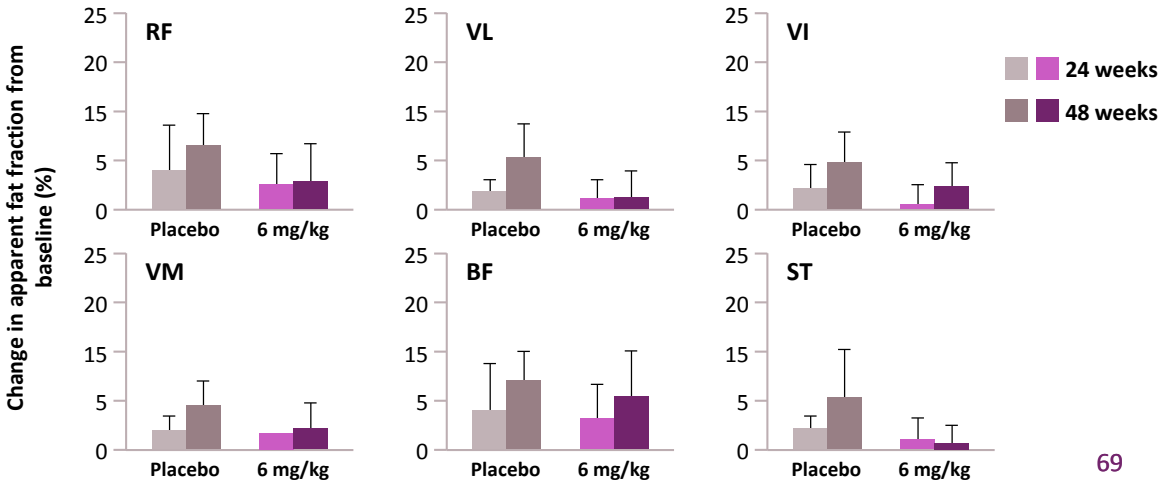






[1]Preliminary analysis; [2]Treatment duration 24 weeks

MRI data suggest reduced fat infiltration*

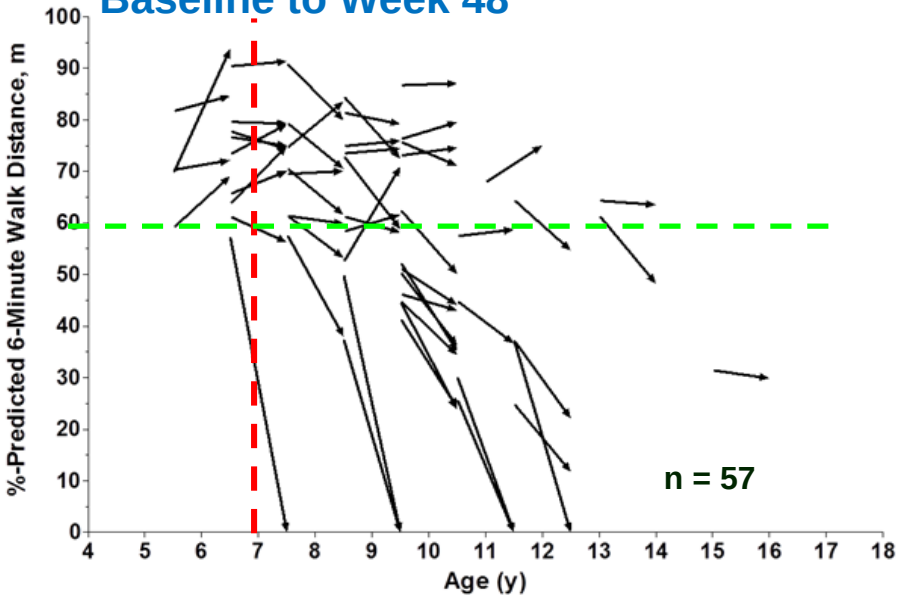


*Subjects were from study DMD114876.
AON, antisense oligonucleotides; BF, bicep femoris; CK, creatine kinase; MRI, magnetic resonance imaging; RF, rectus femoris; ST, semitendinosus; VI, vastus intermedius; VL, vastus lateralis; VM, vastus medialis.

- Prosensa and now Biomarin are leveraging what they have learned from natural history studies to design confirmatory studies of drisapersen in DMD

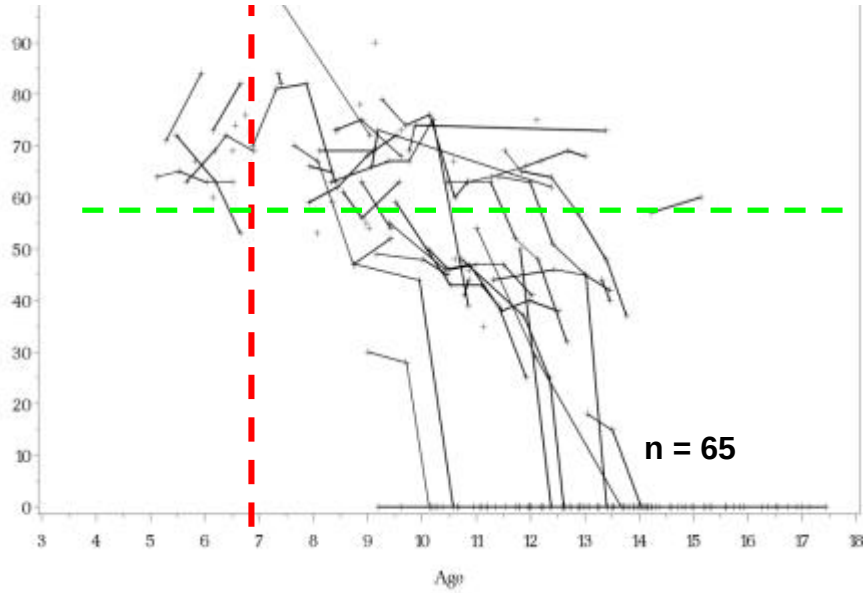
Placebo-control data looks similar to natural history data over 48 weeks

Placebo Data: Ataluren Trial
37 sites (Change in %-predicted 6MWD)
Baseline to Week 48



Δ -44 m (SD 88)
Δ -7.3% Pred
McDonald et al.
Muscle & Nerve 2013
N = 57

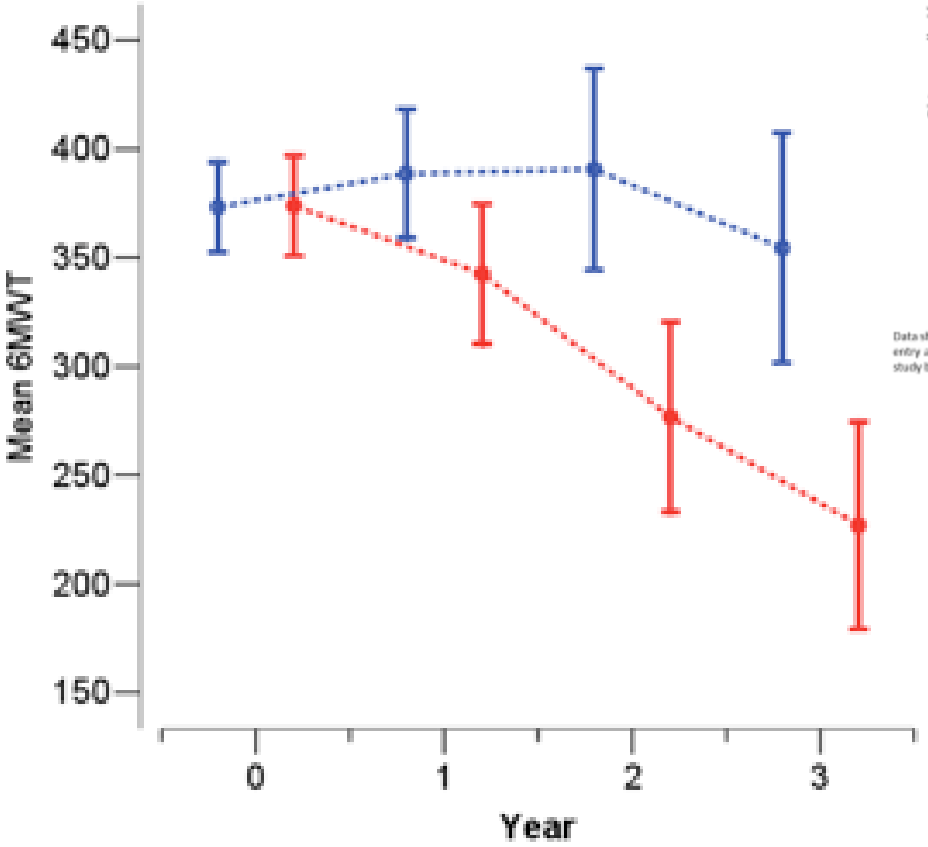
Natural History Data: Belgium
Change %-predicted 6MWD
Baseline to Week 52



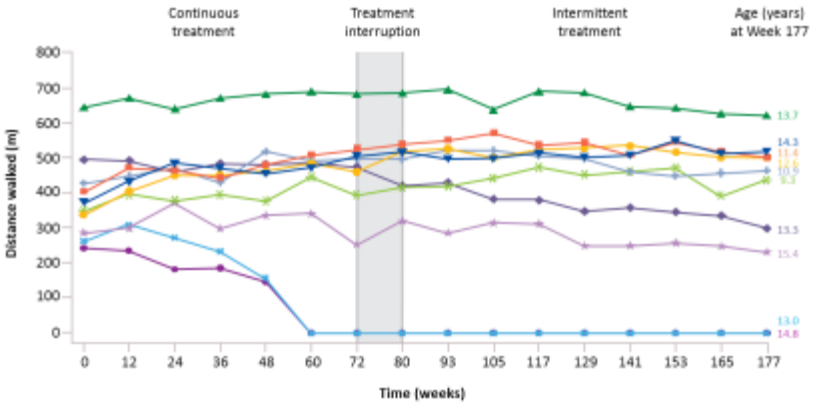
Δ -43 meters (SD 90)
Δ -8.1% Pred.
N. Goemans et al.
Neuromuscular Disorders, 2013
N = 65

Baseline age can predict decline in ambulation in DMD

36 month changes in boys
below 7 years (blue)
above 7 years (red)



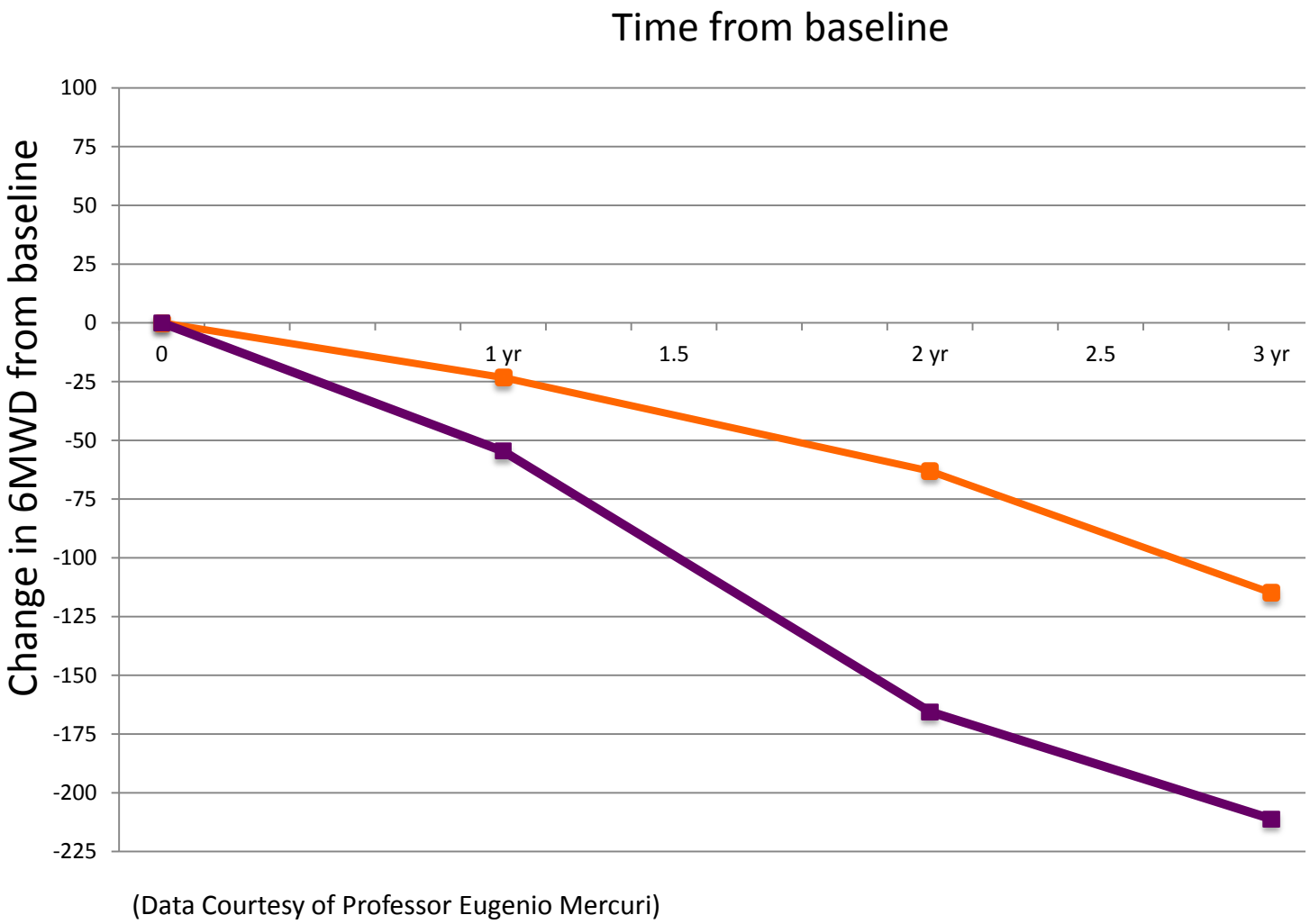
OLE study DMD114673: 6MWD



Data shown are for all subjects who completed the test at extension study baseline. One subject (subject 201) was non-ambulant at study entry and did not participate in any 6MWD tests while another subject (subject 103) was unable to complete the 6MWD test at extension study baseline. Data for both of these subjects are not shown here.

Mazzone *et al.* (PLOS ONE 2014)

Effect of Baseline 6MWD on change in 6MWD
(Data Courtesy of Eugenio Mercuri)

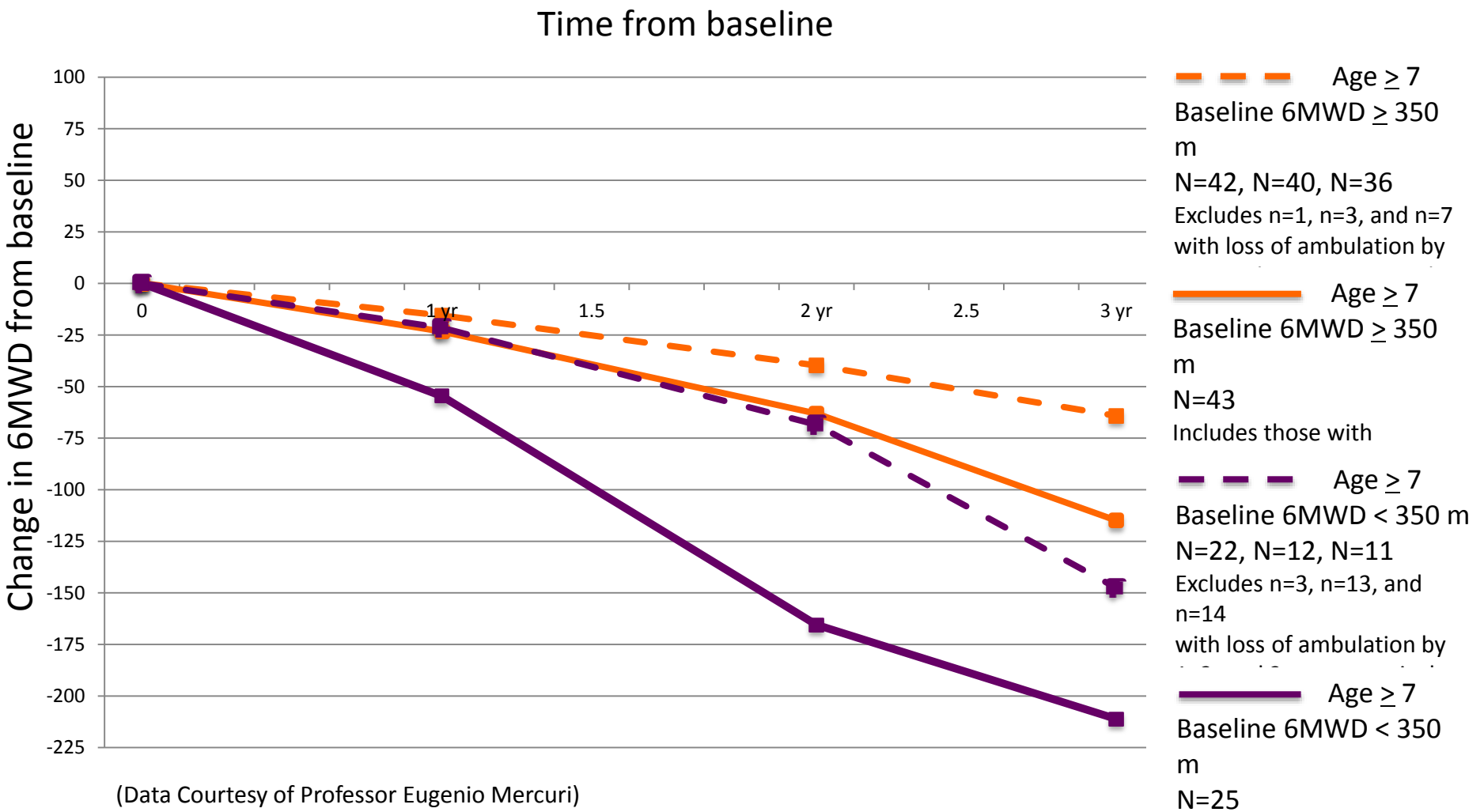


Age ≥ 7
Baseline 6MWD ≥ 350 m
N=43
Includes those with loss of ambulation

Age ≥ 7
Baseline 6MWD < 350 m
N=25
Includes those with loss of ambulation

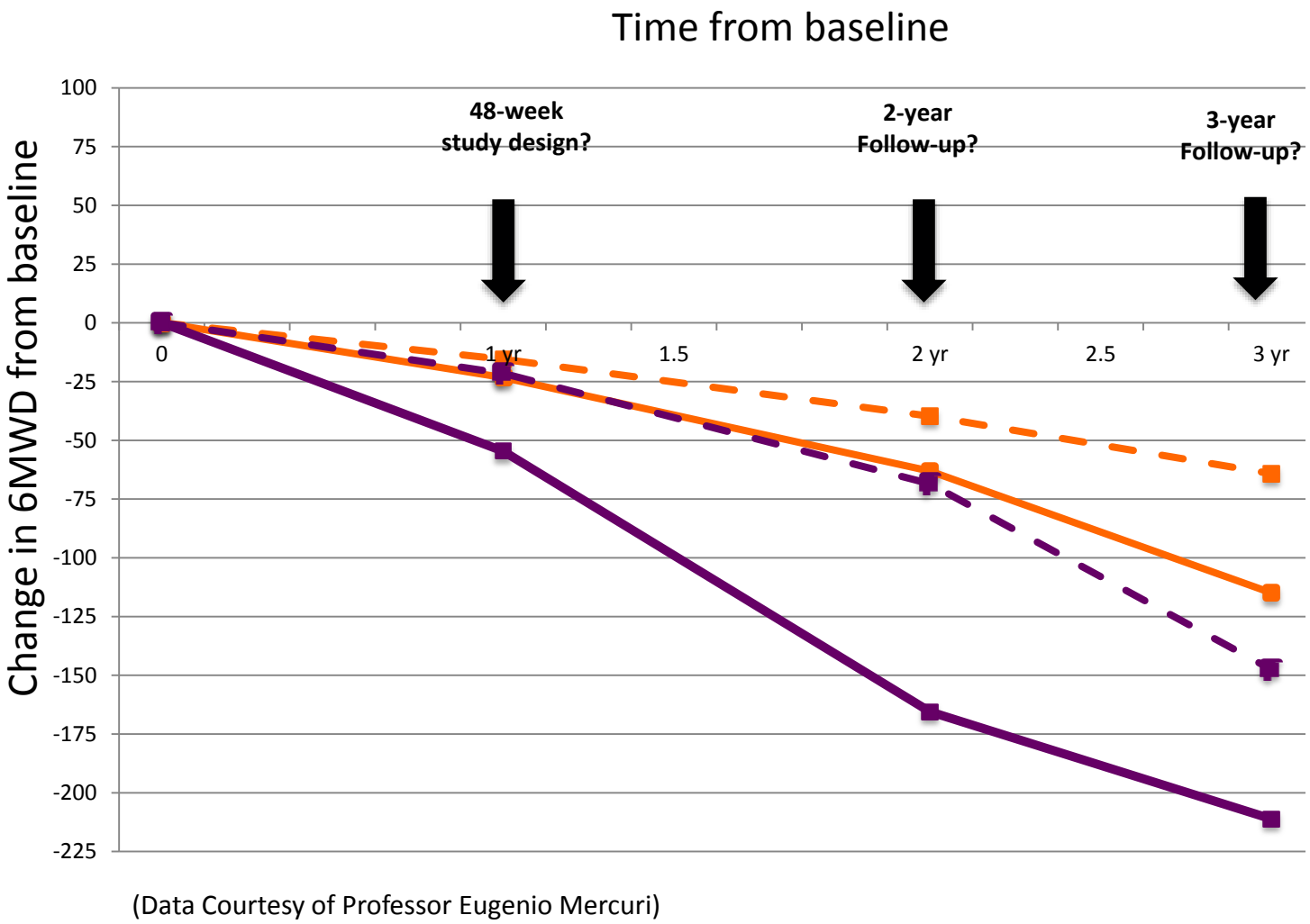
Effect of Baseline 6MWD and Loss of Ambulation on Change in 6MWD

(Data Courtesy of Eugenio Mercuri)



(Data Courtesy of Professor Eugenio Mercuri)

Effect of Baseline 6MWD and Loss of Ambulation
(Data Courtesy of Eugenio Mercuri)



(Data Courtesy of Professor Eugenio Mercuri)

Age ≥ 7
Baseline 6MWD ≥ 350 m
N=42, N=40, N=36
Excludes n=1, n=3, and n=7 with loss of ambulation by 1, 2, and 3 yrs respectively

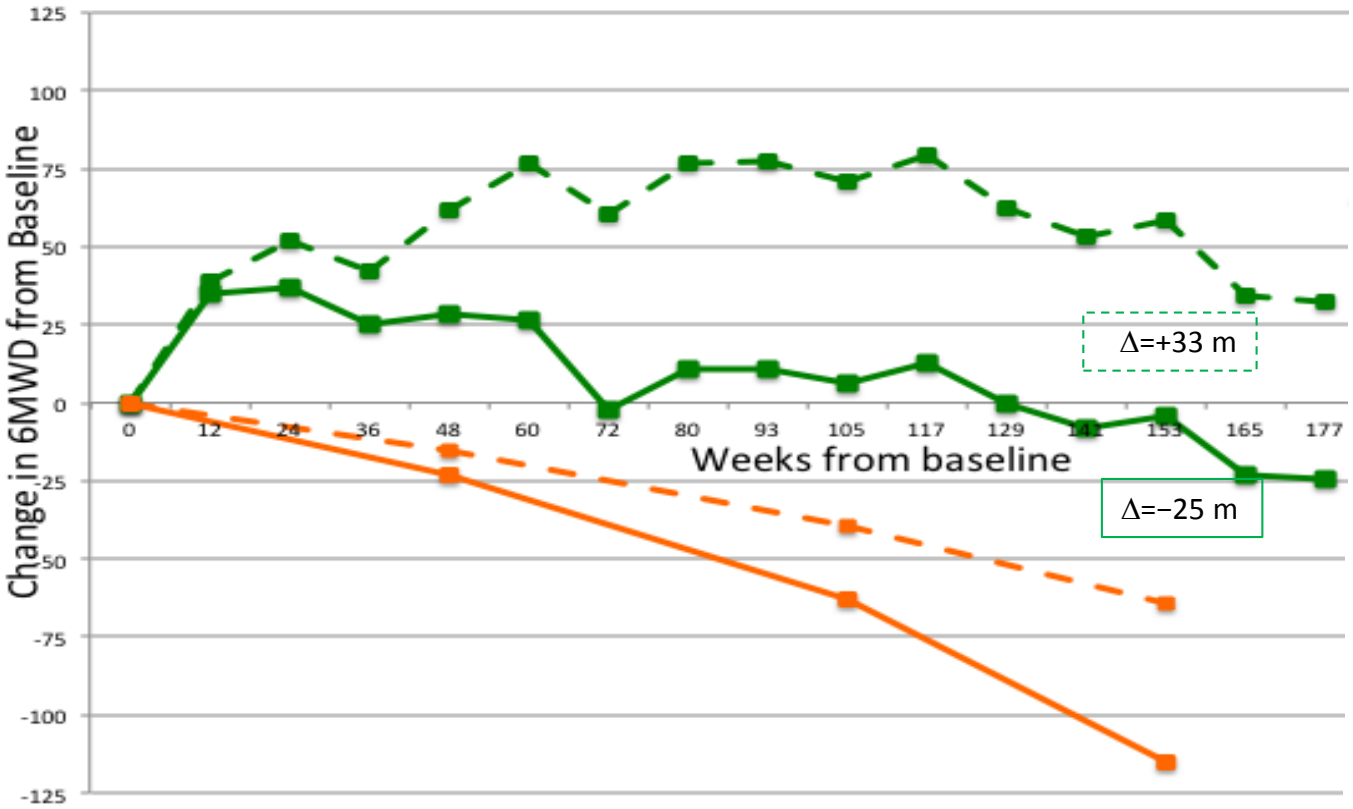
Age ≥ 7
Baseline 6MWD ≥ 350 m
N=43
Includes those with loss of ambulation

Age ≥ 7
Baseline 6MWD < 350 m
N=22, N=12, N=11
Excludes n=3, n=13, and n=14 with loss of ambulation by 1, 2, and 3 yrs respectively

Age ≥ 7
Baseline 6MWD < 350 m
N=25
Includes those with loss of ambulation

DMD114673 vs. Natural History

both including and excluding patients who lost ambulation



DMD114673 Drisapersen 6 mg/kg (n=8)
Baseline 6MWD = 417 m
Excludes n=2 with loss of ambulation

DMD114673 Drisapersen 6 mg/kg (n=10)
Baseline 6MWD = 386 m
Including 2 patients with lost ambulation

Age ≥ 7
Baseline 6MWD ≥ 350 m
N=42, N=40, N=36
Excludes n=1, n=3, and n=7 with loss of ambulation by 1, 2, and 3 yrs respectively

Age ≥ 7
Baseline 6MWD ≥ 350 m
N=43
Includes those with loss of ambulation

†Natural history data provided by Professor Eugenio Mercuri (Catholic University Policlinico Gemelli, Rome, Italy).
Note: Direct comparisons between extension drisapersen from DMD114673 and the natural history data cannot be made. They are presented together for illustrative purposes only.

Safety:

Drisapersen was generally well tolerated

Drisapersen clinical trial program: key safety data

Drisapersen is generally well tolerated, with an adverse event (AE) profile consistent with that described previously for this class of molecule

- **59 serious AEs reported on drisapersen, most considered unrelated : 15/59 serious AEs were considered related or possibly related to drisapersen**
  - 12 of >300 subjects have withdrawn permanently from treatment owing to AEs
- **Most commonly reported AEs include injection-site reactions and renal abnormalities (including subclinical proteinuria)**
  - Some cases of (moderate to severe) thrombocytopaenia have been reported

AEs of special interest, n (%):

Study	Treatment	N	Any AE of special interest	Injection-site reactions*	Renal abnormalities†	Inflammation	Hepatic	Thrombocytes
DMD114117	Placebo	18	13 (72%)	6 (33%)	7 (39%)	9 (50%)	1 (6%)	0
	Drisapersen 6 mg/kg/week	18	16 (89%)	14 (78%)	13 (72%)	10 (56%)	2 (11%)	0
DMD114876	Placebo	16	9 (56%)	5 (31%)	5 (31%)	1 (6%)	1 (6%)	0
	Drisapersen 6 mg/kg/week	18	16 (89%)	13 (72%)	5 (28%)	5 (28%)	1 (6%)	0
DMD114044‡	Placebo	61	37 (61%)	10 (16%)	20 (33%)	16 (26%)	0	0
	Drisapersen 6 mg/kg/week	125	114 (91%)	97 (78%)	80 (64%)	33 (26%)	7 (6%)	0

*Includes discolouration, erythema, rash, induration; †Includes proteinuria, red blood cells in urine; ‡Two subjects in DMD114044 receiving drisapersen 6 mg/kg/week had severe AEs reported by the investigator as drug-related (glomerulonephritis, intracranial venous sinus thrombosis and spinal pain). No severe AEs were reported in the placebo group.

Conclusions

- Comprehensive clinical trial program (>300 subjects) has been conducted to assess safety and efficacy of drisapersen in DMD, comprising both placebo-controlled and OLE studies
- The clinical programme efficacy data suggest:
  - benefit with drisapersen versus placebo in boys with less severe disease
  - clinically meaningful benefit after longer duration of drisapersen treatment in boys who are, on average, more severely affected
- Totality of the data warrant a filing for Accelerated Approval with the FDA and Conditional approval with the EMA

Conclusions

- Prosensa and now Biomarin are leveraging what they have learned from natural history studies to design confirmatory studies of drisapersen in DMD characterized by

  a) choice of the correct dose based on phase 2 studies;

  b) longer trial duration based on our experience with the multiple extension studies; and

  c) an emerging natural history comparison cohort

- Drisapersen was generally well tolerated
  - AEs include sub-clinical proteinuria, local injection-site reactions and thrombocytopenia
  - Addressed by phamacovigilence and emerging dosing regimes (Intermittent dosing after loading; IV route of administration)
  - Overall safety profile is consistent with that described previously for this class of molecule

Q&A



Glenn Pierce, M.D.
Former Chief Medical Officer,
Senior Vice President of Biogen Idec
Hemophilia Therapeutic Area

BIOMARIN ANALYST AND INVESTOR DAY 2014

Hemophilia A: Past, Present and Future Treatment

Glenn Pierce, MD PhD
Independent Consultant
BioMarin Analyst and Investor Day
10 December 2014

Understanding Hemophilia A

Disease Definition	● Hereditary bleeding disorder characterized by a prolonged clotting time due to having substantially reduced or no clotting factor VIII
Epidemiology	● Rare: 1 / 5,000 male births (X-linked); Geography: similar incidence worldwide ● Present at birth; no current cure; ● Only 25-30% of world's patients (~100,000) are diagnosed and treated ● >90% rFVIII is consumed in NA, EU, Japan
Treatment	● Replacement of clotting factor with: (1) whole blood, cryoprecipitate or concentrated plasma-derived products or (2) recombinant factor VIII (preferred) ● "On-demand" (when bleeding) vs. prophylactic (to prevent bleeds before they start, preferred) therapy
Patient sub-groups (vis-à-vis treatment)	● Disease severity: severe, moderate, mild (dependent on percentage of FVIII level in blood, <1%, 1-5%, >5%); 60% of known patients are severe ● Neutralizing antibodies to FVIII are a significant medical complication ● Hemophilia B has an identical phenotype
Other facts	● Treatment is lifelong and costly ● Patients are well organized and educated about their disease ● Strong advocacy due to past history of viral transmission (HIV, HCV, HBV)

Hemophilia Demographics

	Hemophilia A (Classic Hemophilia)	Hemophilia B (Christmas Disease)
Portion of Hemophilic Population	80%	20%
Deficient Clotting Factor in the Body	Factor VIII ("FVIII")	Factor IX ("FIX")
Approx Incidence (CDC)	1 in 5,000 male births	1 in 25,000 male births
Approx Number of Hemophilia Patients in U.S.	16,000	3,300
Identified Patients Globally (WFH)	108,000	22,000
Calculated Expected Global Prevalence	680,000	170,000

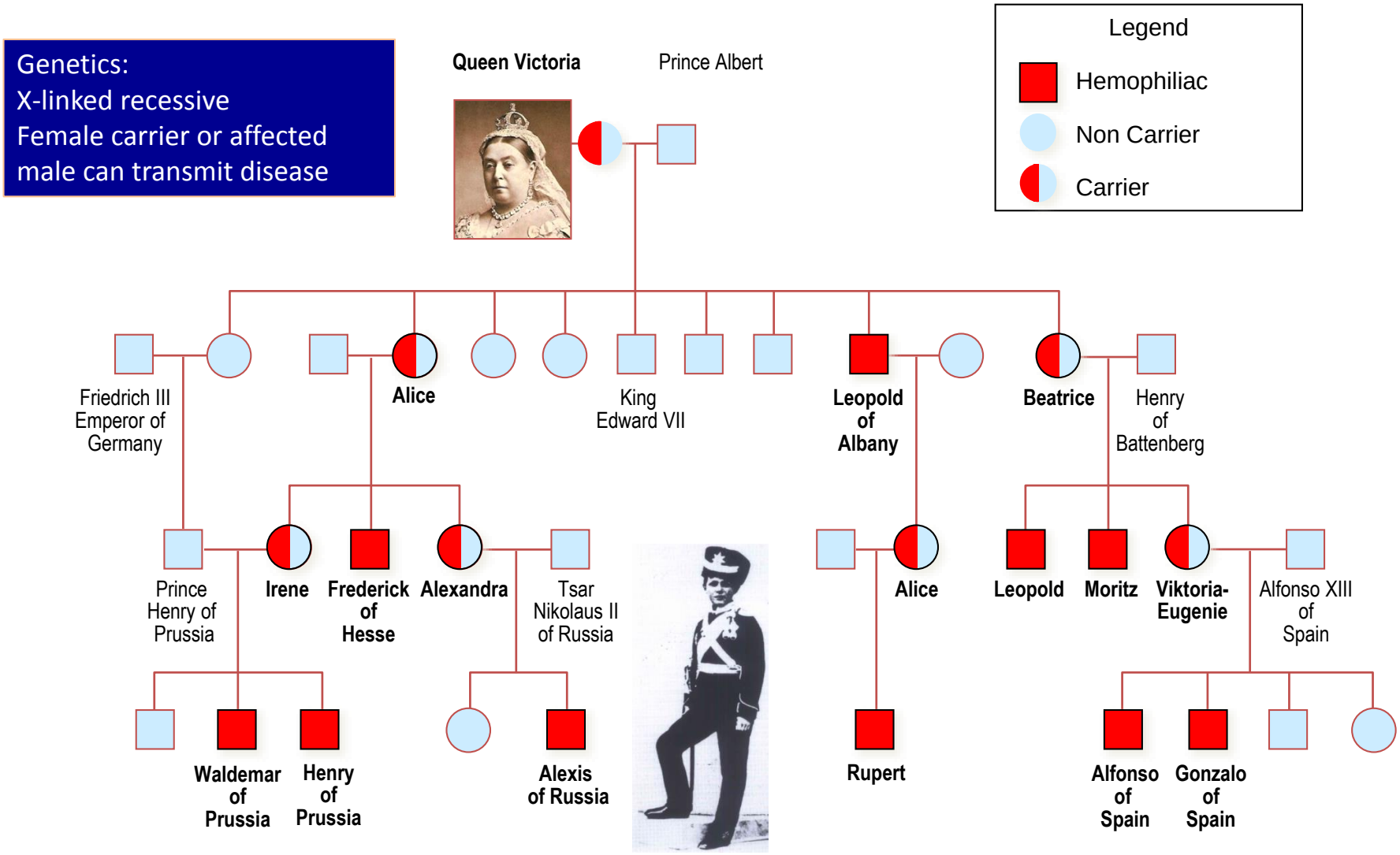
- 70% of patients inherit Hemophilia A and 30% develop spontaneous genetic mutations
- Average annual HemA treatment cost in developed world: $150-300K; weight-based dosing

Source: WFH

Victoria's Secret

Hemophilia Heredity in European Royalty

Genetics:
X-linked recessive
Female carrier or affected male can transmit disease



Rogaev et al, Science 2009: 326:817 Genotype Analysis Identifies the Cause of the "Royal Disease"

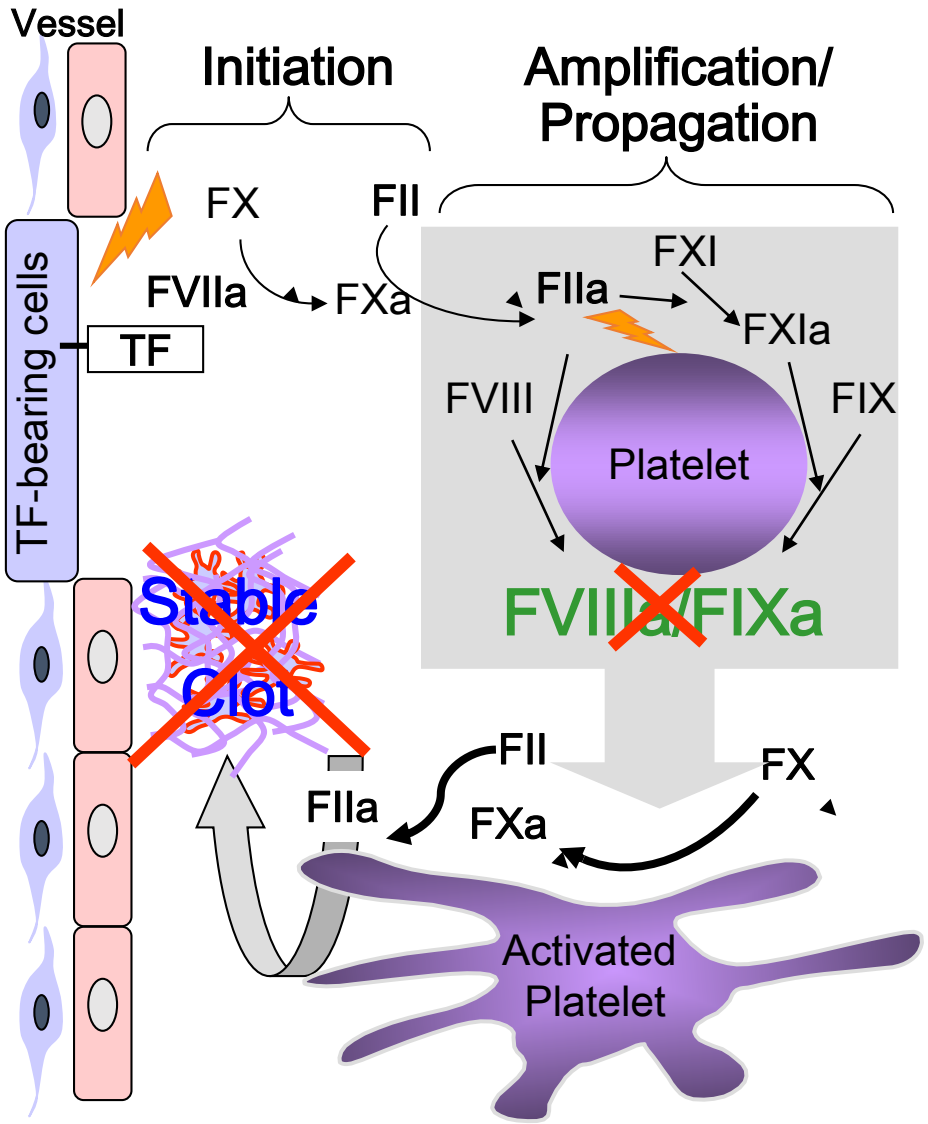
Hemophilia is the Oldest Described Genetic Disorder

“. . .if the first son of a woman is circumcised and he dies and the second son is circumcised and he dies, you must not circumcise the third son. . .

additionally, the sons of the woman’s sister should not be circumcised but the sons of her brother can be circumcised. Talmud (Yebamot 64b)



Coagulation Cascade Simplified



- Tissue Factor (TF) interacts with FVII/FVIIa to initiate clotting. Hemostasis (stable clot) is achieved through amplification of thrombin burst on activated platelets by the FVIIIa/FIXa complex.
- In hemophilia, the FVIIIa/FIXa complex is deficient, thus dampening thrombin burst on activated platelets, resulting in unstable clots and rebleeding.

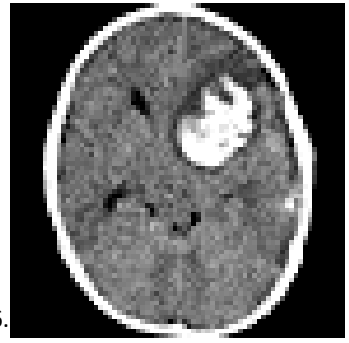
Morbidity and Mortality of Hemophilia A

- Hemarthroses: chronic joint degeneration from recurrent bleeds = target joints
- Bleeding in soft tissues, muscles, GI tract and brain
- Nested case control study of 10,000 patients, 2% had intracranial hemorrhage with 20% mortality rate
- Severe hemophilia A patients have on average 30-50 bleeds per patient year
- Death rate is highly dependent upon access to [1] HTC care and [2] treatment

Clinical outcomes have been favorably impacted by prophylactic replacement therapy, however the required frequent administration is challenging in multiple patient subpopulations








Kulkarni R, Soucie JM.Semin Thromb Hemost. 2011;37:737-44.
Witmer C, Presley R, Kulkarni R, Soucie JM, Manno CS, Raffini L. Br J Haematol. 2011;152:211-6.

Target Joints Create Lifelong Morbidity



Before



After

- Osteoporosis
- Narrowing of joint space
- Overgrowth of epiphyses
- Irregularity of subchondral surfaces

Evolution of Treatment for Patients with Hemophilia



Recombinant Era

1969

1993

Late 1990s

2000s

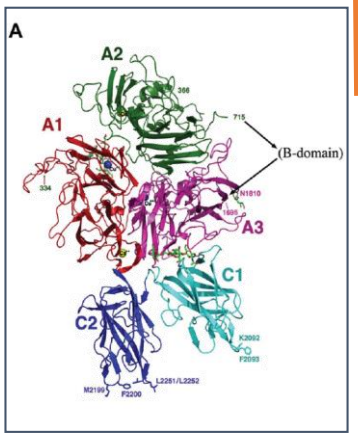
2013-2014

Plasma-derived Factor VIII and Factor IX Concentrates

Widespread viral contamination



rFactor VIIIs





rFactor IX

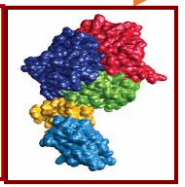
rFactor VIIa

Improved devices for reconstitution

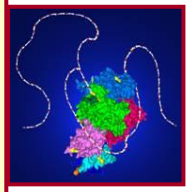




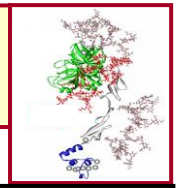
Bio-Similar Factors VIII, IX



Prolonged half life Fusion, PEG FVIII, FIX

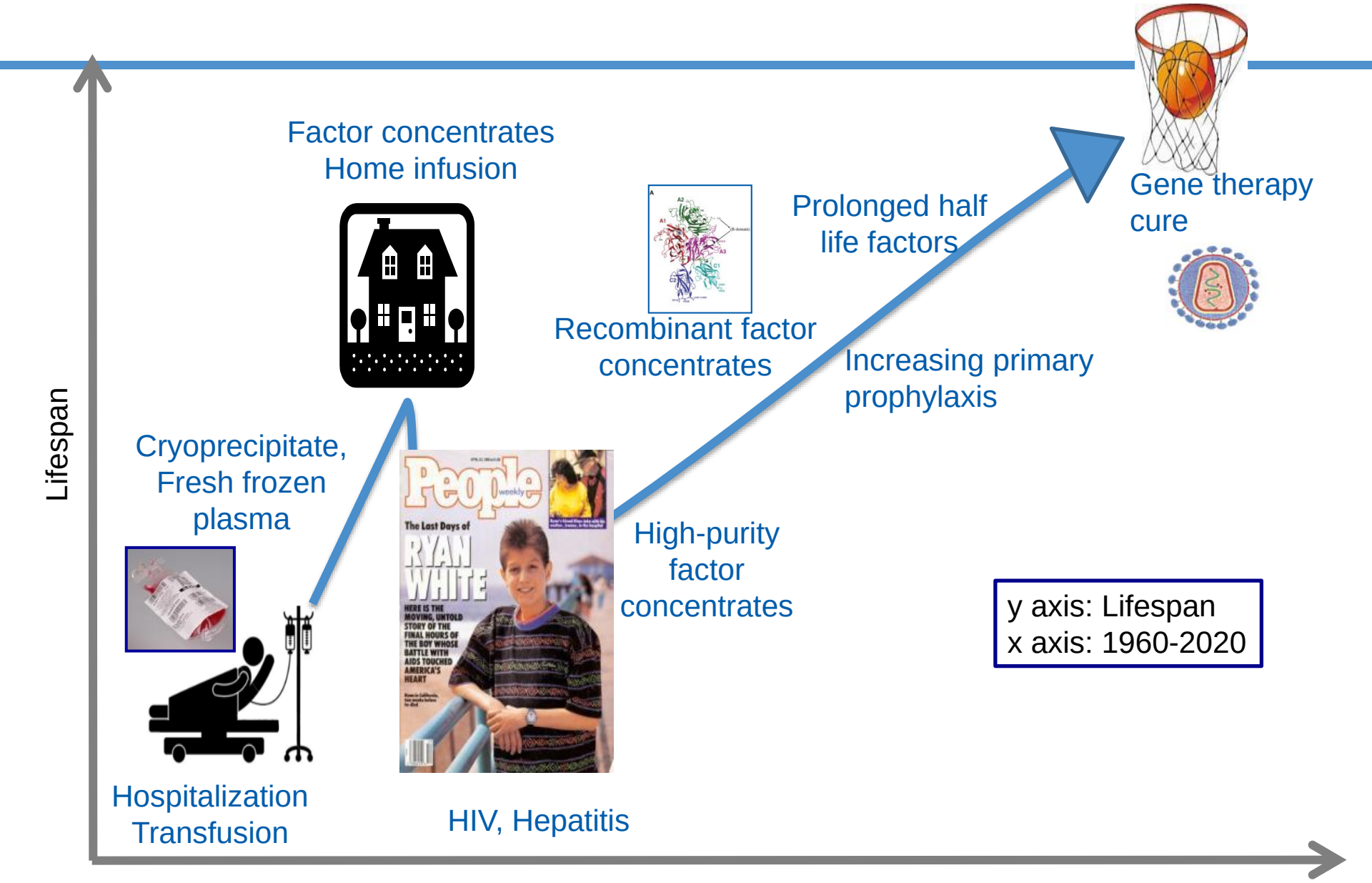


Bypassing agents



Gene Therapies

Advances in Hemophilia Care: The Past Six Decades



Hemophilia A Requires Frequent Intravenous Injections of Replacement Factor VIII

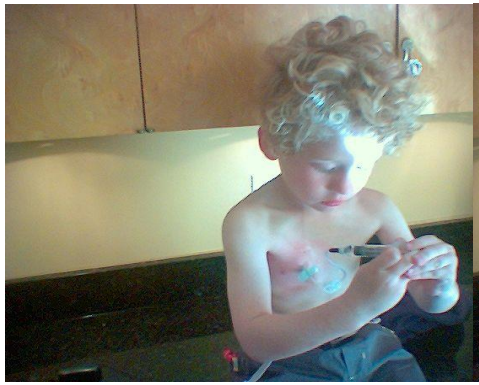


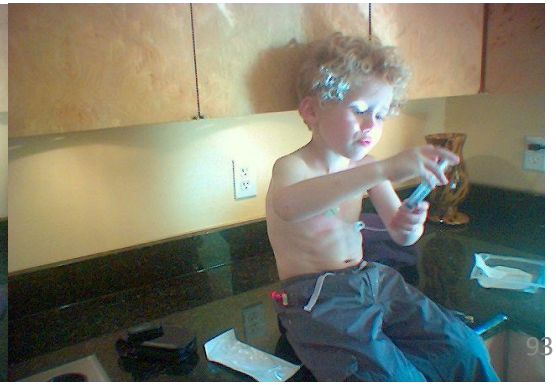






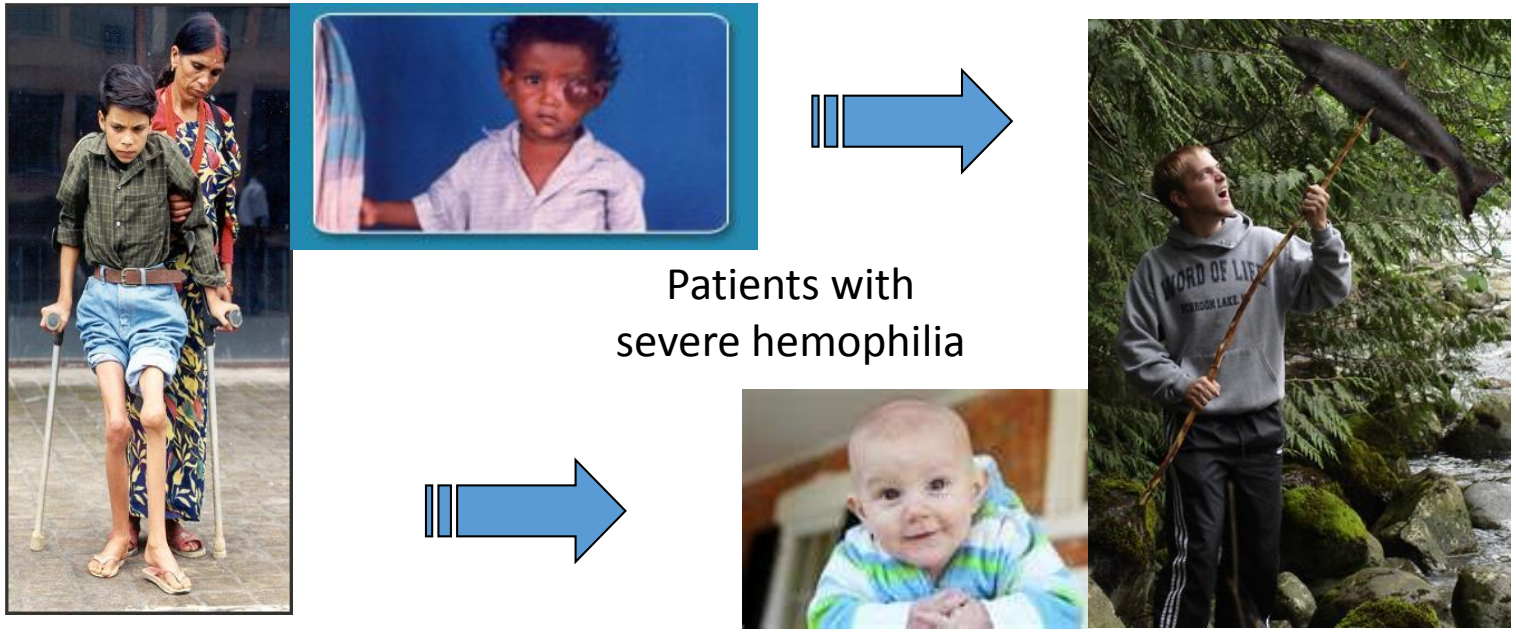
- Injections via family, health care providers, or self
  - Children learn self-infusion at summer camps
- Venipuncture and intravenous administration at home
  - Central venous catheters often required in young children; high infection rates and local thrombosis
- Frequency of administration is highly variable among patients:
  - **Episodic –** FVIII injections to stop individual bleeding episodes (30-50/year)
  - **Prophylaxis –** Periodic infusions to maintain a minimum FVIII level to prevent bleeding
    - FVIII, 3-4x/week, ~150-180/year
    - FIX, 2x/week, ~104/year





Benefits of Prophylaxis

- Proven reduction in bleeding frequency
- Proven preservation of joint structure in young patients
- May reduce other morbidities (*e.g.,* ICH)
- May reduce risk of inhibitor formation when started early
- May improve quality of life and productivity
- May reduce healthcare utilization



Manco-Johnson MJ et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. N Engl J Med. 2007 Aug 9;357(6):535-44.

Challenges of Subclinical Bleeding



Some joints with no clinically recorded hemorrhages had high MRI scores, whereas some joints with more than 10 hemorrhages did not show bone or cartilage damage on MRI

Valentino JTH, 2010;8:1895-02

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 9, 2007 VOL. 357 NO. 6

Prophylaxis versus Episodic Treatment to Prevent Joint Disease in Boys with Severe Hemophilia

Brenda R
Michael L.
W. Keith
Deborah Br
Alisor
Alexis

3 points:

Primary prophylaxis works

Subclinical bleeding causes damage

Repair process highly variable

BACKGROUND

Effective ways to prevent arthropathy in severe hemophilia are unknown.

METHODS

We randomly assigned young boys with severe hemophilia A to regular infusions of recombinant factor VIII (prophylaxis) or to an enhanced episodic infusion schedule of at least three doses totaling a minimum of 80 IU of factor VIII per kilogram of body weight at the time of a joint hemorrhage. The primary outcome was the inci-

Authors' affiliations are listed in the Appendix. Address reprint requests to Dr. M.J. Manco-Johnson, Mountain States Regional Hemophilia and Thrombosis Center, MS F-416, PO Box 6507, Aurora, CO 80045, or at marilyn.manco-johnson@uchsc.edu.

N Engl J Med 2007;357:535-44.

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Bleeding in Hemophilia A is inversely related to factor levels

- Repeated joint bleeds lead to arthropathy, pain, and loss of joint function

- <1 %normal FVIII level
  Frequent bleeding episodes
- >5% normal FVIII level
  - 83% fewer bleeds but still at risk for trauma-induced bleeds

"The aim of FVIII gene transfer is sustained long-term factor production at levels >5% that would effectively convert severely affected patients to a milder phenotype."

Walsh & Batt 2013 Trans Res 161:307

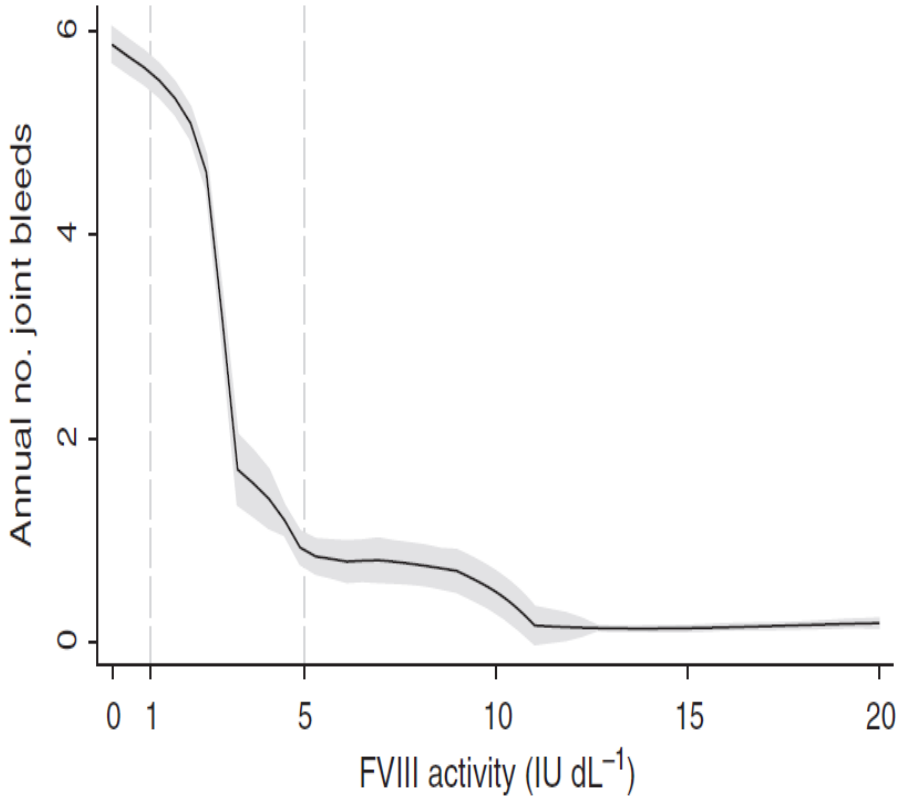


Fig. 2. Annual number of joint bleeds according to FVIII activity. Black lines are medians, shaded areas interquartile ranges.

den Uijl IE et al; 2011 Haemophilia 17: 849-853; den Uijl IE, Fischer K, Van Der Bom JG, Grobbee DE, Rosendaal FR, Plug I. Haemophilia. 2011; 17:41-4.

Next Era: Prolonged Half Life Products as the Next Advance Before Gene Therapy

blood

Prepublished online November 13, 2013;
doi:10.1182/blood-2013-10-529974

Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A

Johnny Mahlangu, Jerry S. Powell, Margaret V. Ragni, Pratima Chowdary, Neil C. Josephson, Ingrid Pabinger, Hideji Hanabusa, Naresh Gupta, Roshni Kulkarni, Patrick Fogarty, David Perry, Amy Shapiro, K. John Pasi, Shashikant Apte, Ivan Nestorov, Haiyan Jiang, Shuanglian Li, Srividya Neelakantan, Lynda M. Cristiano, Jaya Goyal, Jurg M. Sommer, Jennifer A. Dumont, Nigel Dodd, Karen Nugent, Gloria Vigliani, Alvin Luk, Aoife Brennan and Glenn F. Pierce

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Study of Recombinant Factor IX Fc Fusion Protein in Hemophilia B

Jerry S. Powell, M.D., K. John Pasi, M.B., Ch.B., Ph.D., Margaret V. Ragni, M.D., M.P.H., Margareth C. Ozelo, M.D., Ph.D., Leonard A. Valentino, M.D., Johnny N. Mahlangu, M.D., M.Med., Neil C. Josephson, M.D., David Perry, M.D., Ph.D., Marilyn J. Manco-Johnson, M.D., Shashikant Apte, M.D., Ross I. Baker, M.D., Godfrey C. Chan, M.D., Nicolas Novitzky, M.D., Ph.D., Raymond S. Wong, M.D., Snejana Krassova, M.D., Geoffrey Allen, M.D., Haiyan Jiang, Ph.D., Alison Innes, B.Sc., Shuanglian Li, M.D., Ph.D., Lynda M. Cristiano, M.D., Jaya Goyal, Ph.D., Jurg M. Sommer, Ph.D., Jennifer A. Dumont, Ph.D., Karen Nugent, M.Sc., Gloria Vigliani, M.D., Aoife Brennan, M.B., B.Ch., Alvin Luk, Ph.D., and Glenn F. Pierce, M.D., Ph.D. for the B-LONG Investigators

N Engl J Med 2013; 369:2313-2323 | December 12, 2013 | DOI: 10.1056/NEJMoa1305074

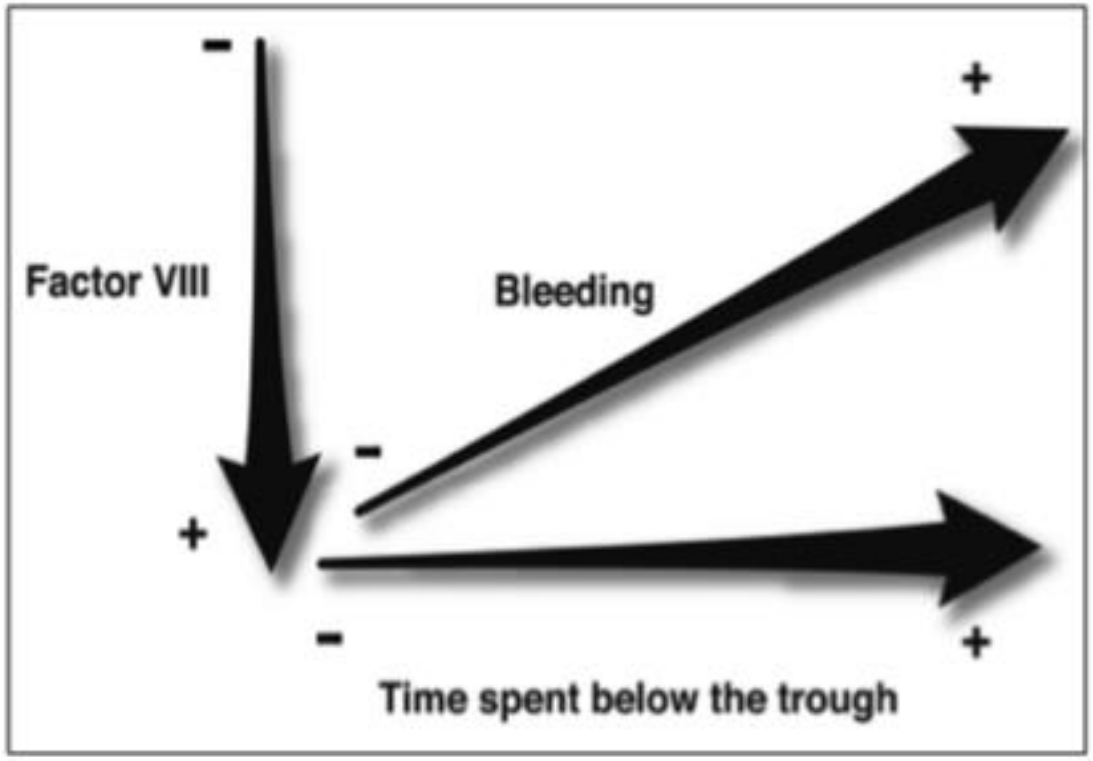
Status: Unmet Needs in Hemophilia Treatment

- Substantial morbidity in hemophilia patients remains
  - Development of inhibitors (Neutralizing antibodies)
  - Infections and thrombosis from central venous catheters
  - Disabling joint disease in individuals in absence of prophylaxis
- Safety and availability of therapy have improved, now focus of care has shifted to prevention of disease sequelae
  - Higher than 1% trough levels required
  - 10-15% troughs will prevent all bleeding except major trauma
- Longer-lasting, less immunogenic, and more easily administered therapies needed; ultimately,
- A cure

Fogarty PF. *Hematol Am Soc Hematol Educ Program*: 2011:397-404; Berntorp E, Shapiro AD. *Lancet*. 2012;379:1447-1456; Mitragotrii S, PA Burke, R Langer. (2014) *Nature Reviews Drug Discovery* 13:9, 655-672; M. Carcao. 2014; *Haemophilia* 20, 99-105; Manco-Johnson MJ, et al. N Engl J Med. 2007;357(6):535-44; Gringeri A, et al. J Thromb Haemost. 2011;9:700-10; Manco-Johnson MJ, et al. J Thromb Haemost. 2013; Mar 25. doi: 10.1111/jth.12202; Skinner MW, Myles E. Haemophilia. 2013;19:475-80

98

Factor Level, Bleeding, and Time Below Trough



Bleeding is a function of FVIII activity level and time spent below 1% trough

Jiménez-Yusti, Blood Transfus 2014; ***12****: 314-9* DOI 10.2450/2014.0298-13

What's Next?
Rationale for FVIII Gene Therapy

Maintain factor level >1% with prophylactic therapy prevents most (but not all) bleeding and attenuates chronic arthropathy.







Native recombinant Factor VIIIs have a short half-life; thus patients require dosing 3-4 times/week (156 – 208 injections per year)



Prolonged half life FVIII decreases injections and may increase compliance. Patients dose 1-2 times/week (52-104 injections per year); Or more frequently and achieve higher troughs

Gene therapy may offer a route toward a cure, which obviates all or most of the injections required to prevent bleeding

Potential Benefits of Gene Therapy

- Freedom from frequent injections
  - Improve outcomes- sustained bleeding protection at higher trough levels
  - Eliminate nonadherence to prophylaxis
  - QoL- normalized physical activities
- Other potential benefits of a cure via gene therapy
  - Eliminate infusion-related co-morbidities and preserve venous access
  - Eliminate or greatly reduce total factor consumption
- Freedom from disease due to higher circulating trough levels of FVIII compared to native and engineered FVIII
  - With a serious, chronic genetic disease like hemophilia, the risk of injury is omnipresent 24/7, every waking minute of every day. Freedom from this burden is an unimaginable paradigm shift in existence

Berntorp E, Shapiro AD. *Lancet*. 2012;379:1447-1456; Lillicrap D. *Curr Opin Hematol*. 2010;17:393-397;3Gater A et al. *Thromb Haemost*. 2011;106:398-404; Berntorp E. *Haemophilia*. 2009;15:1219-1227; Pipe SW. *Hematol Am Soc Hematol Educ Program*. 2010;2010:203-209; High KA.
Hematology Am Soc Hematol Educ Program. 2012;2012:375-81; High KH, Nathwani A, Spencer T, Lillicrap D. Haemophilia. 2014 May;20 Suppl 4:43-9.`

Gene Transfer Human Trials in Hemophilia –

Round 1

***All first-in-class** *** Demonstrated safety but not efficacy** ***Basis for next studies**

Hemophilia A	**12 subjects**	**Ex vivo electroporation of autologous fibroblasts, reimplantation onto peritoneum**
Hemophilia A	**13 subjects**	**Intravenous infusion of retroviral vector expressing BDD-FVIII**
Hemophilia A	**1 subject**	**Helper-dependent (fully deleted) adenoviral vector expressing full-length FVIII under albumin promoter**

Gene Transfer Human Trials in Hemophilia –

Round 2 – The Power of Iterative science

New vector

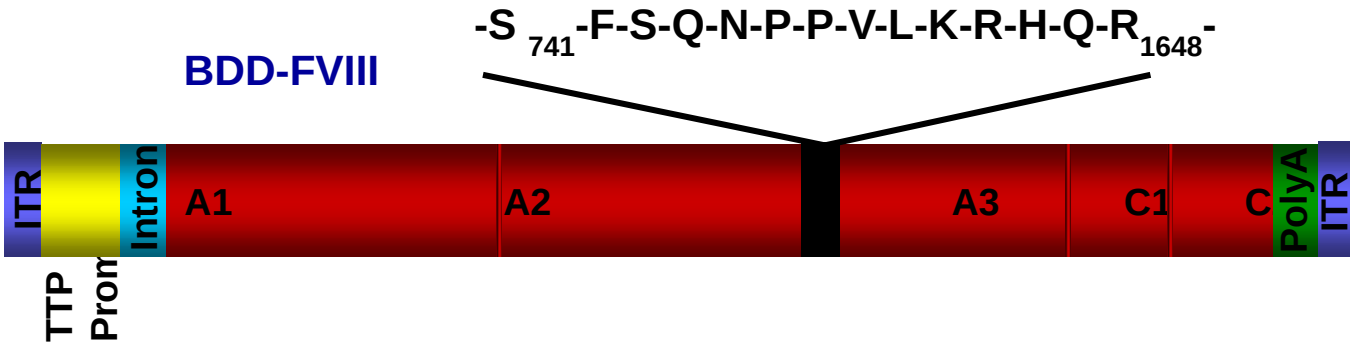
New gene

New promoter

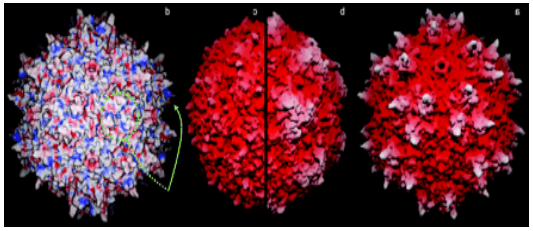
Greater preclinical success

Clinical proof of principle

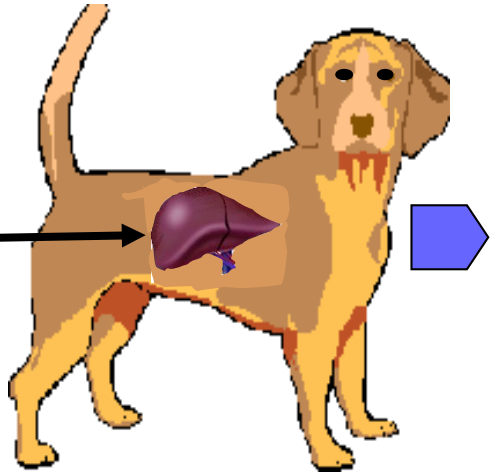
Long-term Factor VIII Production Following Liver-Directed AAV Gene Therapy in Hemophilia A dogs



AAV2, 6, 8 - FVIII



Via portal vein into liver



- **2- 5% canine FVIII (>3 yr)**
- **Normalized WBCT**
- **No longer bleed**
- **No toxicity**
  - No inhibitor to FVIII
  - No CTL to AAV

Jiang, Lillicrap, Pierce, Blood 2006, 108:107-115

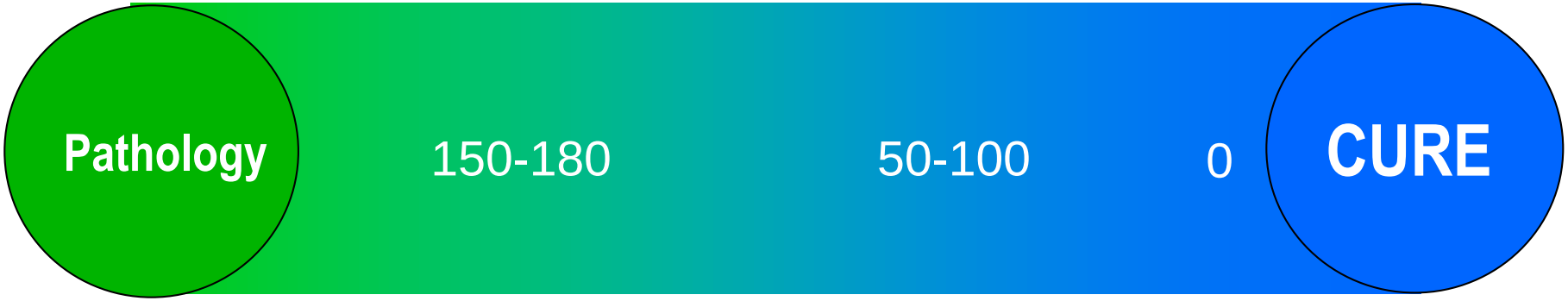
- **Insufficient levels for clinical development**

- **Sufficient levels for clinical development**

Nathwani Lab: McIntosh et al Blood. 2013;121(17):3335-3344)

Hemophilia: Inevitable March Towards a Cure

Understanding the pathology of hemophilia (eg, hemophilic arthropathy, mortality) has led to a push from symptomatic therapy toward treatment to prevent bleeds to a call for higher troughs



Symptomatic treatment: on-demand therapy-1970s	**Regular, preventative treatment-1990s**	**Reduced infusion frequency and/or higher troughs-2010s**	**Curative therapy-2020s**



BMN 270 FOR HEMOPHILIA A

BIOMARIN ANALYST AND INVESTOR DAY 2014

Barrie Carter, PhD, VP, Vector Biology
BioMarin

Gene Therapy is a Great fit for BioMarin

Strategic synergies:

- Historical strength in use of enzymes to replace genetic defect
- Logical extension to replace genetic defect with a gene
- Gene delivery is an alternate form of protein replacement

Hemophilia A selected as BioMarin's entry point into gene therapy:

- Clinical success with hemophilia B by University College London (UCL)
- BioMarin license of Hemophilia A technology from UCL

Internal expertize

- Gordon Vehar, VP Research at BioMarin, FVIII
- Barrie Carter, VP Vector Biology, AAV vectors

Proof-of-Concept Demonstrated in Hemophilia B

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 22, 2011 VOL. 365 NO. 25

Adenovirus-Associated Virus Vector–Mediated Gene Transfer in Hemophilia B

Amit C. Nathwani, M.B., Ch.B., Ph.D., Edward G.D. Tuddenham, M.B., B.S., M.D., Savita Rangarajan, M.B., B.S., Cecilia Rosales, Ph.D., Jenny McIntosh, Ph.D., David C. Linch, M.B., B.Chir., Pratima Chowdary, M.B., B.S., Anne Riddell, B.Sc., Arnulfo Jaquilmac Pie, B.S.N., Chris Harrington, B.S.N., James O'Beirne, M.B., B.S., M.D., Keith Smith, M.Sc., John Pasi, M.D., Bertil Glader, M.D., Ph.D., Pradip Rustagi, M.D., Catherine Y.C. Ng, M.S., Mark A. Kay, M.D., Ph.D., Junfang Zhou, M.D., Yunyu Spence, Ph.D., Christopher L. Morton, B.S., James Allay, Ph.D., John Coleman, M.S., Susan Sleep, Ph.D., John M. Cunningham, M.D., Deokumar Srivastava, Ph.D., Etiena Basner-Tschakarjan, M.D., Federico Mingozzi, Ph.D., Katherine A. High, M.D., John T. Gray, Ph.D., Ulrike M. Reiss, M.D., Arthur W. Nienhuis, M.D., and Andrew M. Davidoff, M.D.

Experience in AAV Vectors

MOLECULAR AND CELLULAR BIOLOGY, Oct. 1984, p. 2072–2081
0270-7306/84/102072-10$02.00/0
Copyright © 1984, American Society for Microbiology
Vol. 4, No. 10

A Human Parvovirus, Adeno-Associated Virus, as a Eucaryotic Vector: Transient Expression and Encapsidation of the Procaryotic Gene for Chloramphenicol Acetyltransferase

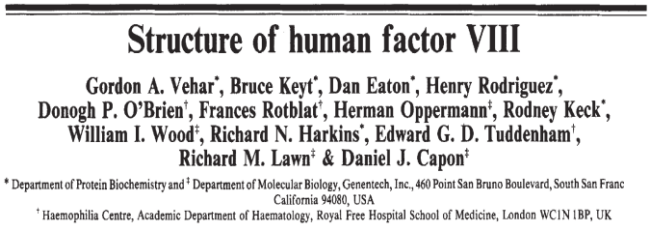
JON-DURI TRATSCHIN, MICHAEL H. P. WEST, TRACEY SANDBANK, AND BARRIE J. CARTER*

Laboratory of Cell Biology and Genetics, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, Bethesda, Maryland 20205

Received 3 April 1984/Accepted 2 July 1984

Mol Cell Biol 4:2072 October 1984

Human FVIII Processing in vivo

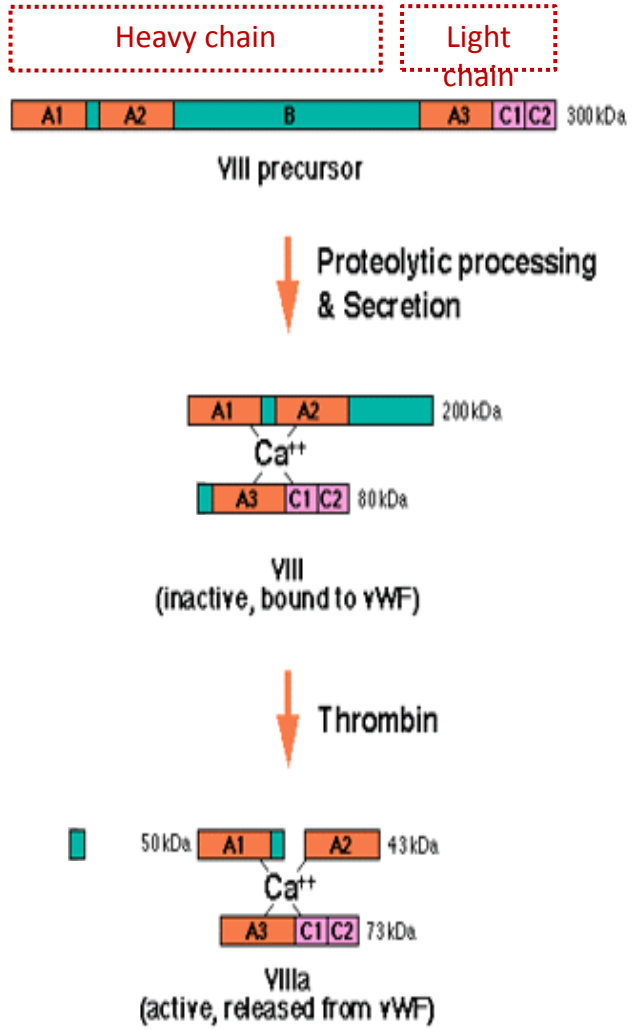


Structure of human factor VIII

Gordon A. Vehar*, Bruce Keyt*, Dan Eaton*, Henry Rodriguez*, Donogh P. O'Brien†, Frances Rotblat†, Herman Oppermann‡, Rodney Keck*, William I. Wood‡, Richard N. Harkins*, Edward G. D. Tuddenham†, Richard M. Lawn‡ & Daniel J. Capon‡

* Department of Protein Biochemistry and ‡ Department of Molecular Biology, Genentech, Inc., 460 Point San Bruno Boulevard, South San Franc California 94080, USA
† Haemophilia Centre, Academic Department of Haematology, Royal Free Hospital School of Medicine, London WC1N 1BP, UK

- Large gene with over 200 disease alleles
- Intron 22 inversion in 45% of severe cases
- Synthesized as a pre-cofactor
- Thrombin activation into light and heavy chains complexed by Ca^{++}
- C2 interacts with phospholipids, FXa, vWF and thrombin
- B domain not functional in secreted factor VIII, but N-glycosylation role in expression
- B-domain deleted factor VIII is fully functional and is approved (Refacto/Xyntha)



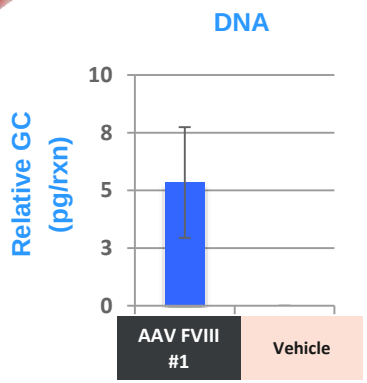
Evaluation of FVIII Gene Therapy

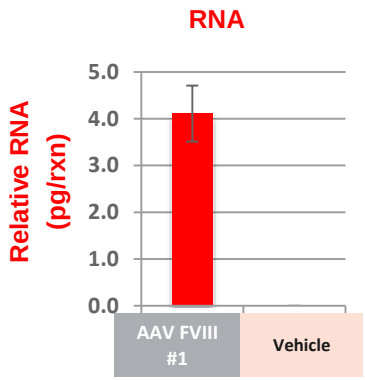
In Wild-type and FVIII-KO Mice

EVALUATION OF AAV FVIII CONSTRUCT #1 IN WILD-TYPE MICE



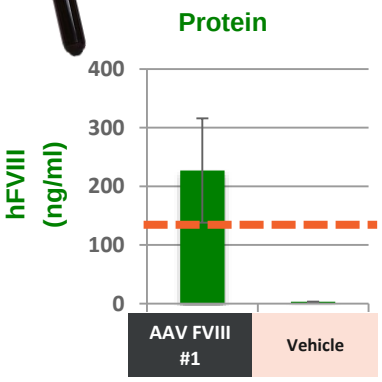
Assessment in Liver Tissue

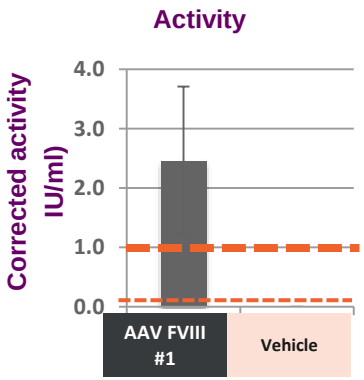






Assessment in Plasma

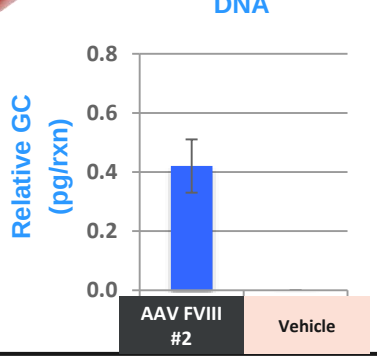


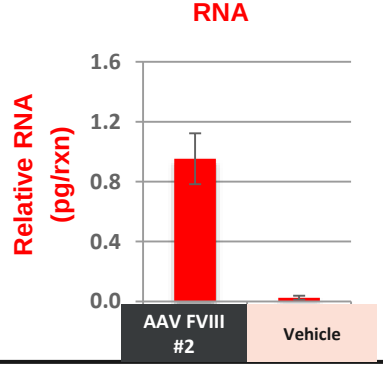


EVALUATION OF AAV FVIII CONSTRUCT #2 IN HEMOPHILIAC MICE



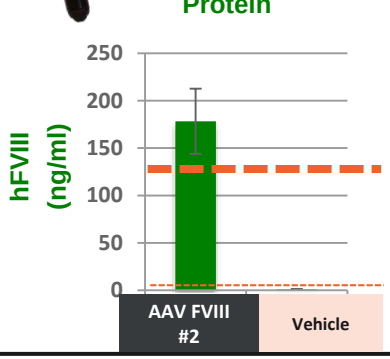
Assessment in Liver Tissue

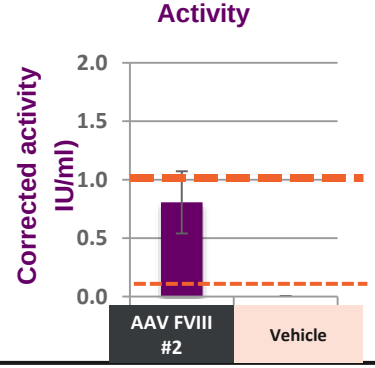






Assessment in Plasma

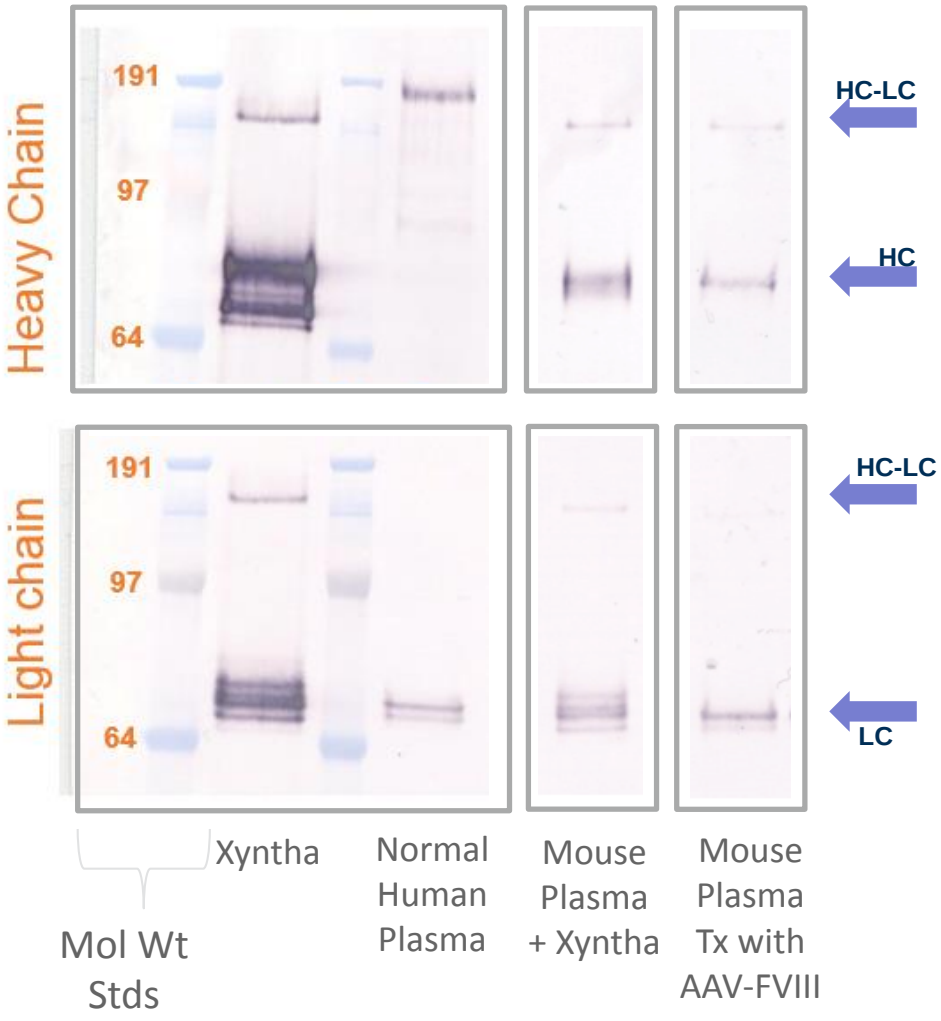




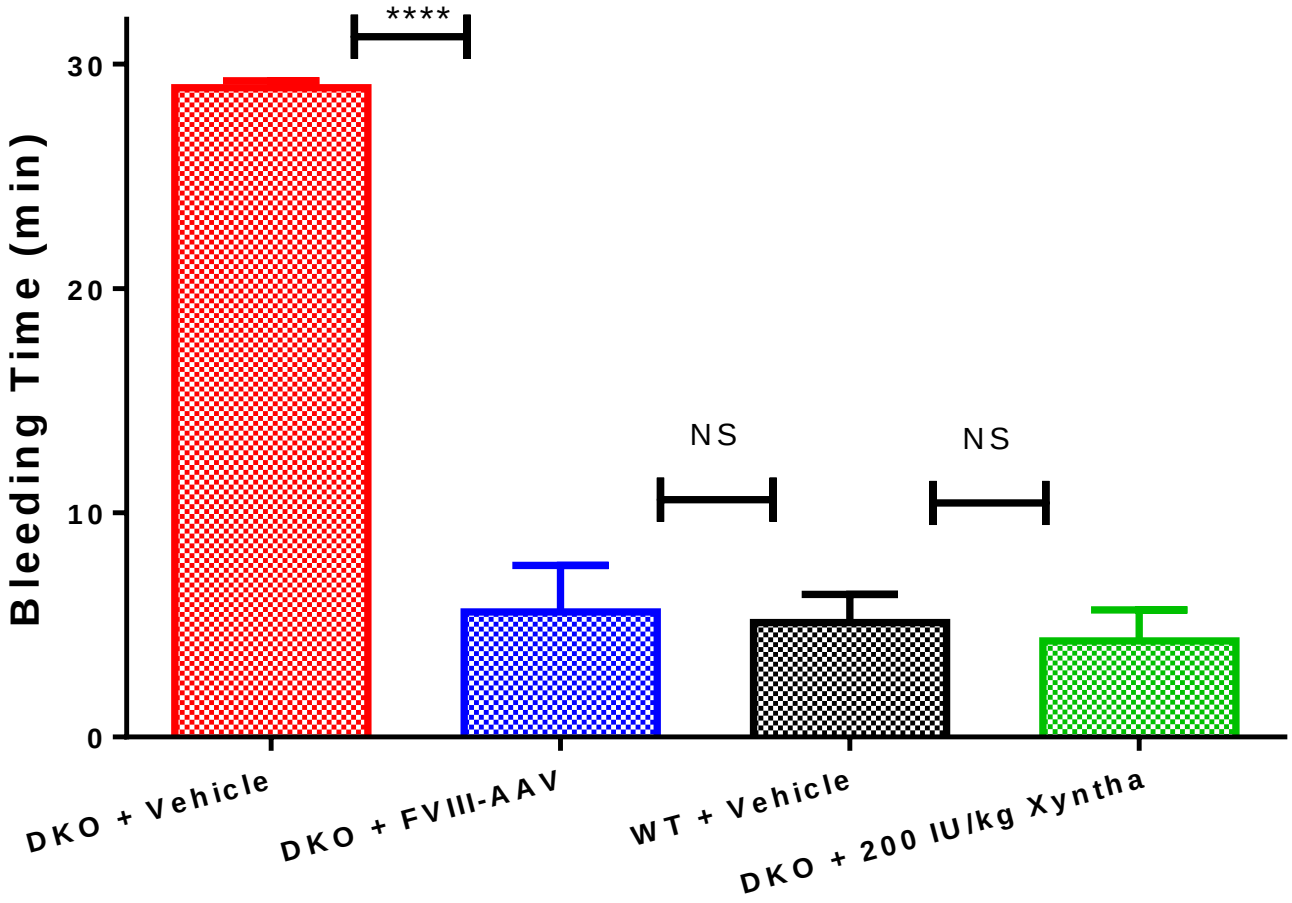
Non-clinical Studies at BioMarin

Animal species/ parameter	capsid	cassette	expression	activity
Wt mice	✓	✓	✓	✓
FVIII KO Mice	✓	✓	✓	✓
Rag2 Mice	✓	✓	✓	✓
FVIII KO/Rag2	✓	✓	✓	✓
monkeys	✓	✓	✓	✓

AAV-FVIII Expresses the Correct huFVIII Protein in Mice



AAV-FVIII Corrects Bleeding Time Defect in Hemophilia Mice



Nonclinical studies: Summary

- Last year we showed you initial mouse data
- Have done a very large amount of additional work
- The correct FVIII protein is expressed
- This shows functional benefit in a surgery challenge model

Status of Clinical Candidate Announced 1Q14

BMN 270 for Hemophilia A -- AAV Factor VIII Vector

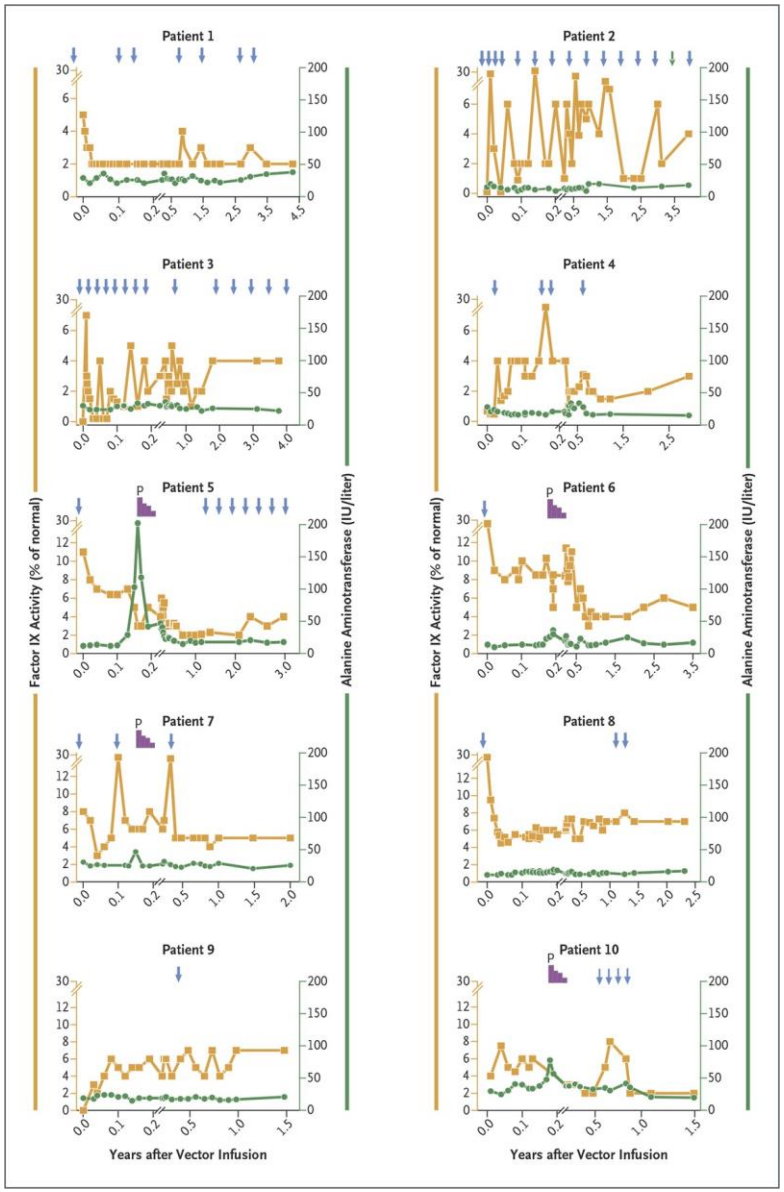
Next Steps

- Complete CTA-enabling studies in 2014
- Regulatory filing for initial clinical trial in 1Q15

Considerations for Clinical Trial

- Main: Determine the dose curve
- Secondary: Transaminitis
- Tertiary: Immunogenicity of expressed transgene
- POC from hemophilia B trials
- Tapered dose steroid if needed
- Subjects with no inhibitor from prior prophylaxis

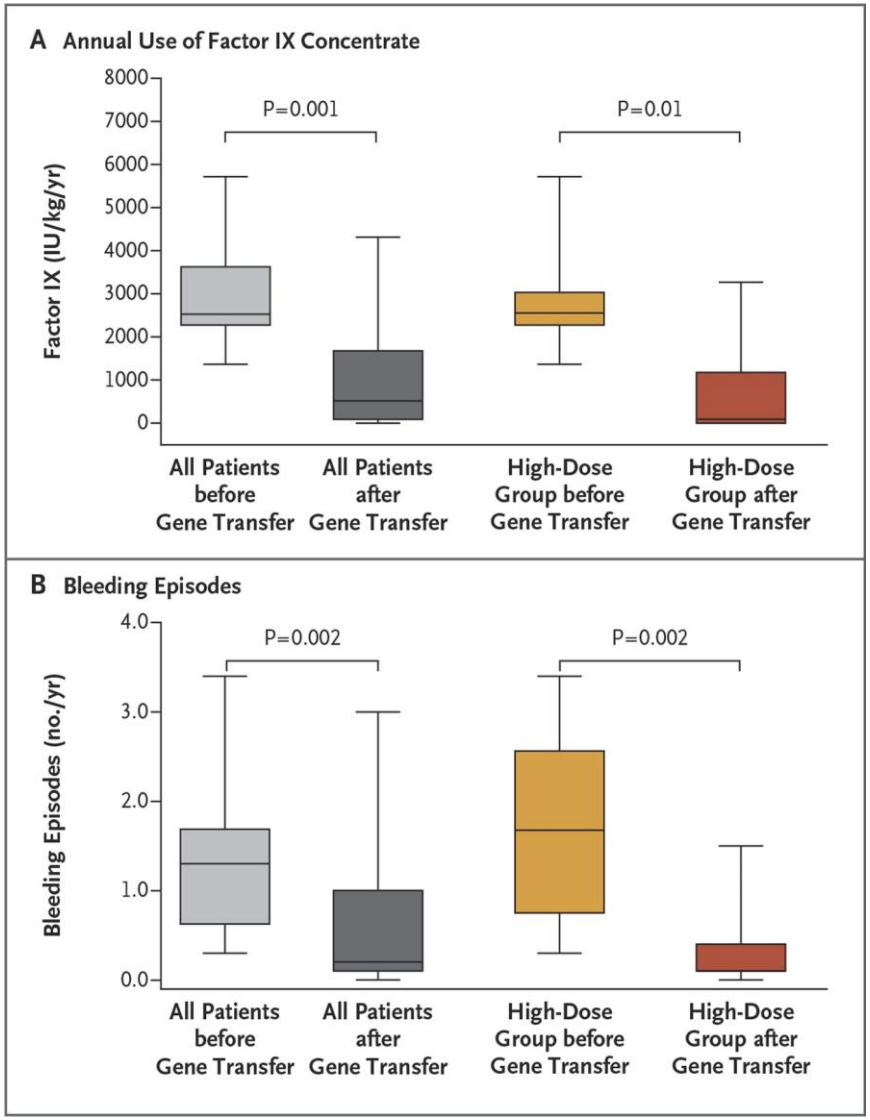
Summary of Factor IX Activity and Liver Function after Vector Infusion in 10 Patients with Hemophilia B



The NEW ENGLAND JOURNAL of MEDICINE

Nathwani et al. N Engl J Med 2014;371:1994-2004

Effect of Gene Transfer on the Administration of Factor IX Concentrate and the Number of Bleeding Episodes before and after Gene Transfer



The NEW ENGLAND JOURNAL of MEDICINE

Nathwani et al. N Engl J Med 2014;371:1994-2004 Med 2014;371:1994-2004

Q&A



BMN 111 FOR ACHONDROPLASIA

BIOMARIN ANALYST AND INVESTOR DAY 2014

Leonid Katz, MD, Senior Medical Director
BioMarin

Achondroplasia – Disease Background

- Most common form of human dwarfism
  - 1 in 15,000 to 25,000 births with ~ 200 new cases/year in the US
- Characterized by abnormal linear bone growth and disproportionate short stature due to proximal shortening of the limbs
- Autosomal dominant activating mutation in the fibroblast growth factor receptor 3 (FGFR3) gene
  - 80% are the result of a spontaneous mutation
- FGFR3 is one of many physiological regulators of linear bone growth which normally functions as an inhibitor, acting negatively on both proliferation and terminal differentiation of growth plate chondrocytes

ACHONDROPLASIA
FGFR3 mutation: abnormalities of chondrogenesis and endochondral bone formation

BODY FUNCTIONS & STRUCTURES

- **Mental functions**
  - Cognitive performance
- **Structures of the nervous system resulting in;**
  - Hydrocephalus
  - Cervicomeduallary compression
  - Hypotonia
- **The eye, ear and related structures resulting in;**
- Altered hearing and vestibular functions
  - Otitis media
- **Structures of the cardiovascular, immunological and respiratory systems resulting in;**
- Altered functions of the respiratory systems
  - Restrictive and obstructive lung disease
- **Structures related to movement resulting in;**
- Altered functions of the joints and bones
  - Bony deformity
  - Soft tissue contracture
  - Spinal deformity
  - Macrocephaly
  - Short limbed short stature
  - Midface hypoplasia
  - Kyphosis
  - Joint hypermobility
  - Reduced muscle strength
  - Secondary obesity

ACTIVITY and PARTICIPATION

- **Learning and applying knowledge**
- Performance at school
- **Communication**
- Development of communication milestones
- Social cognition
- **Mobility**
- Development of gross motor activities
- Development of fine motor activities
- **Self-care**
- Development of independent self-care skills
- Development of eating and drinking skills
- **Major life areas**
- Education
- **Community, social and civic life**
- Recreation and leisure

ENVIRONMENTAL FACTORS

- **Products and technology**
- Lack of equipment, furniture, toys matching anthropometric limitations
- **Natural environment and human-made changes to environment**
- Interaction between body size and environment
- **Support and relationships**
- Family, teachers, community groups
- **Attitudes**
- Societal attitudes
- **Services, systems and policy**
- Attitudes and beliefs of family and community

PERSONAL FACTORS

Model of Achondroplasia From Ireland P. et al. Optimal management of complications associated with achondroplasia, *Applications of Clinical Genetics, 2014*

BMN 111 for Achondroplasia

- BMN 111 is a 39 amino acid, modified recombinant human C-type natriuretic peptide (CNP)
- Mimics CNP pharmacologic activity on bone growth and is resistant to neutral endopeptidase
- Longer half-life than native CNP
- Lyophilized powder for solution for injection

BMN 111 Program Update

- 111-101: First in Man Healthy Adult Study (Completed)
- 111-901: A Multicenter, Multinational Clinical Assessment Study for Pediatric Patients with Achondroplasia (Ongoing)
  - Non-interventional Baseline Growth and Natural History Study
  - 9 sites, 4 countries (US, UK, France, Australia), 76 subjects enrolled
  - After 6 months of baseline growth assessments, subjects can enroll in a study with BMN-111
- 111-202: A Phase 2, Open-label, Sequential Cohort Dose-Escalation Study of BMN 111 in Children with Achondroplasia (Ongoing)
  - First patient enrolled January 2014
  - Data on first three cohorts Q2 2015

BMN 111-901

A Multicenter, Multinational Clinical Assessment Study for Pediatric Patients with Achondroplasia

Baseline Growth and Natural History Study

Baseline Growth and Natural History Study (BMN 111-901)

Objectives

- Characterize baseline growth in children with achondroplasia
- Establish baseline for studies with BMN 111

Study Design

- Growth measurements collected at 3 month intervals until enrollment in treatment study
- 6 months study participation is required prior to enrollment into drug studies to obtain baseline growth velocities
- There is no study drug treatment

Children with Achondroplasia Have Short Stature and Lower Growth Velocity

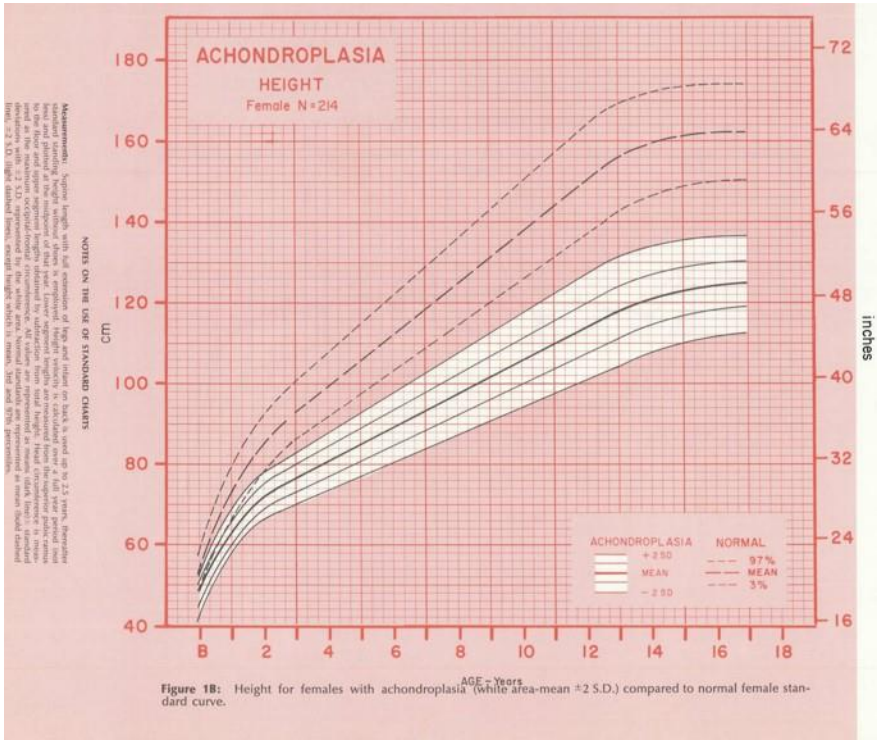


Figure 1B: Height for females with achondroplasia (white area-mean ±2 S.D.) compared to normal female standard curve.

Height

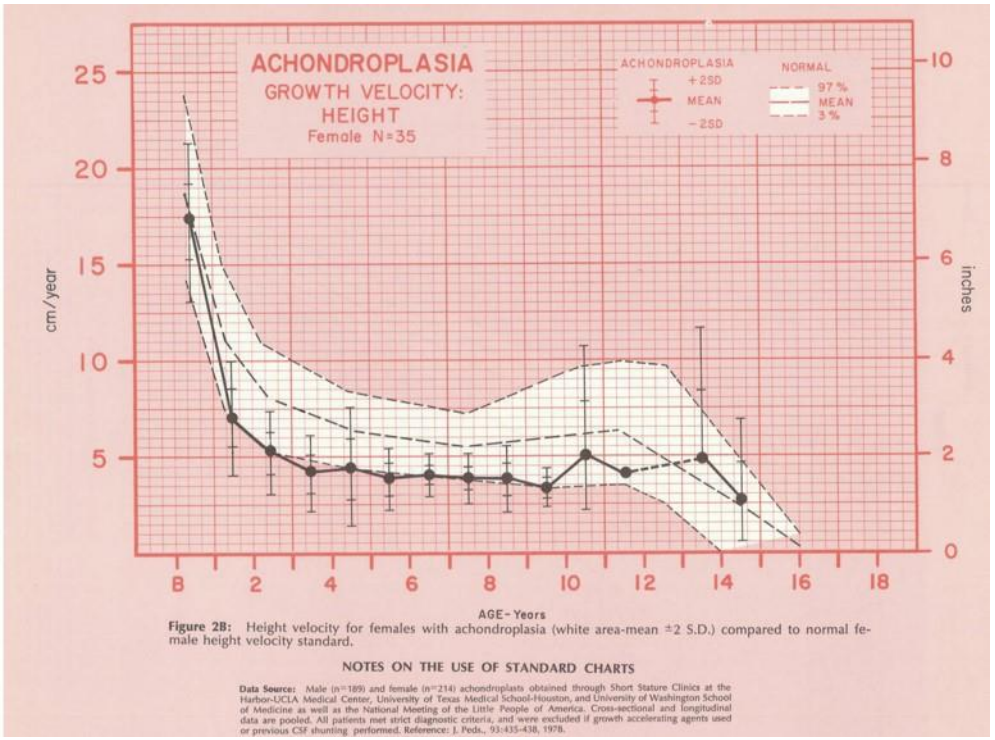


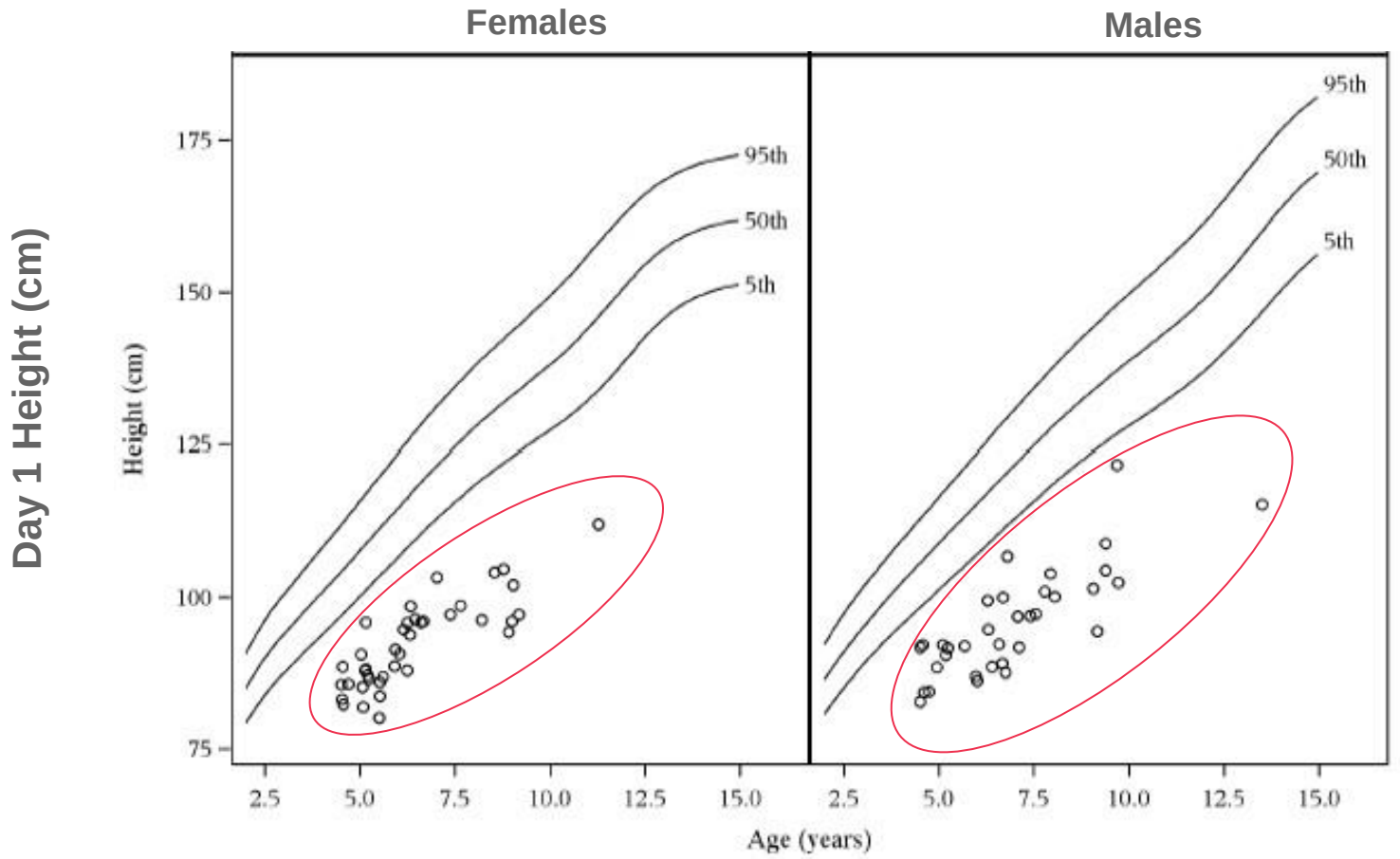
Figure 2B: Height velocity for females with achondroplasia (white area-mean ±2 S.D.) compared to normal female height velocity standard.

Growth velocity

Horton W. et. al. The Journal of Pediatrics, 1978

Baseline Growth and Natural History Study (BMN 111-901)

Height with Age-Gender-Specific CDC References

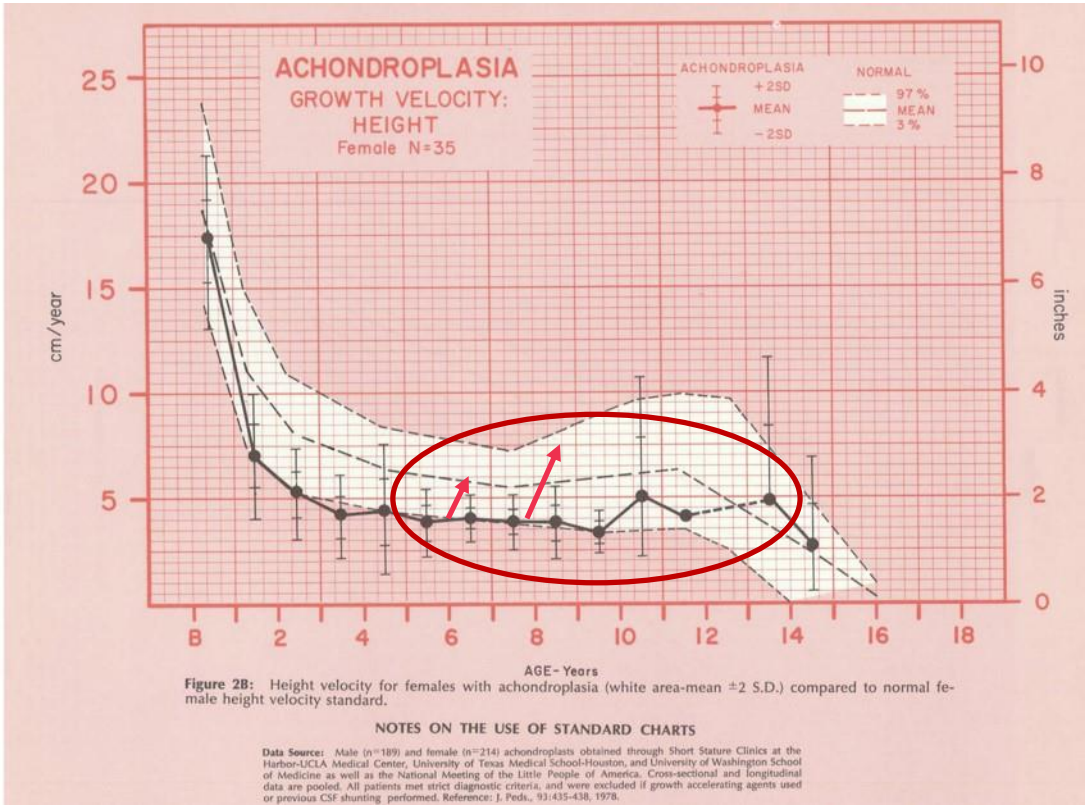


Baseline Growth and Natural History Study (BMN 111-901)

Growth Velocity Summary

	Parameter	Males	Females	Overall Population
	n	33	38	71
Age	Mean (SD)	7.0 (2.00)	6.4 (1.64)	6.7 (1.82)
Growth Velocity 6 months	Mean (SD)	2.1 (0.89)	2.4 (0.89)	2.2 (0.90)
	Median	1.9	2.6	2.2
	Min, Max	1, 4	0, 4	0, 4
Annualized Growth Velocity (cm/yr)	Mean (SD)	4.2 (1.80)	4.7 (1.80)	4.5 (1.80)
	Median	3.8	5.2	4.5
	Min, Max	2, 8	0, 8	0, 8

How Much Growth is Needed?

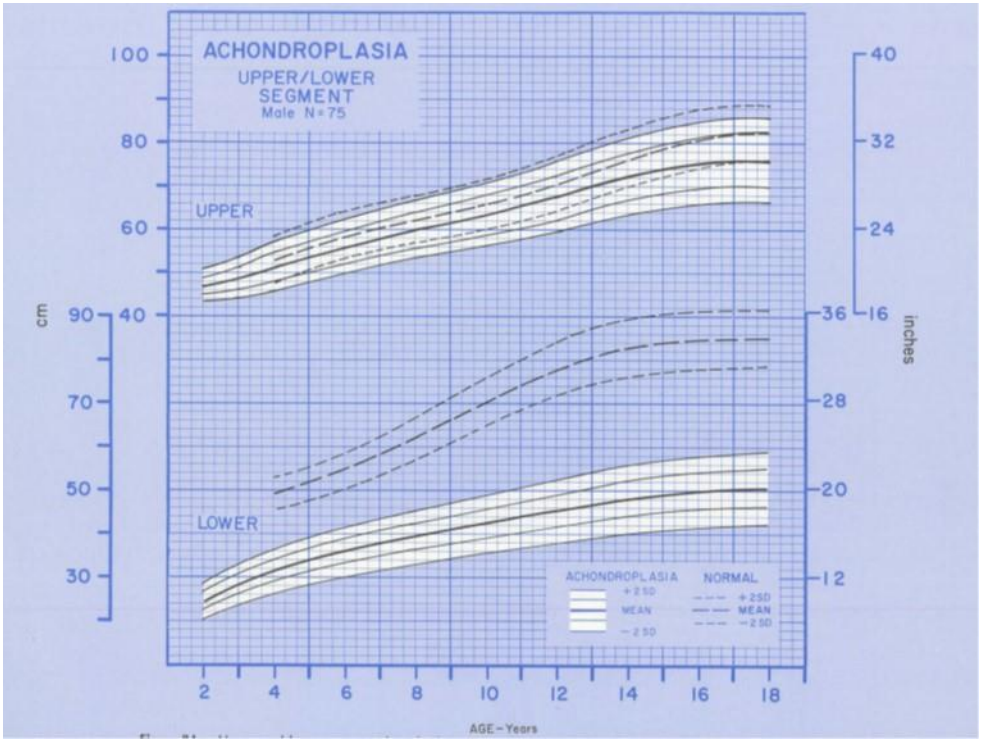


Horton W. et. al. The Journal of Pediatrics, 1978

- With 50% increase in mean growth velocity, children with achondroplasia will approach mean growth velocity of average stature children
- With 80% or greater increase in mean growth velocity, children with achondroplasia could attain mean growth velocity greater than the mean height velocity of average stature children

Greater increase in growth velocity (if sustained over time) could allow reaching a greater final height, potentially approaching mean height for average stature

Disproportionate Growth is a Feature of Achondroplasia



Upper segment - Trunk

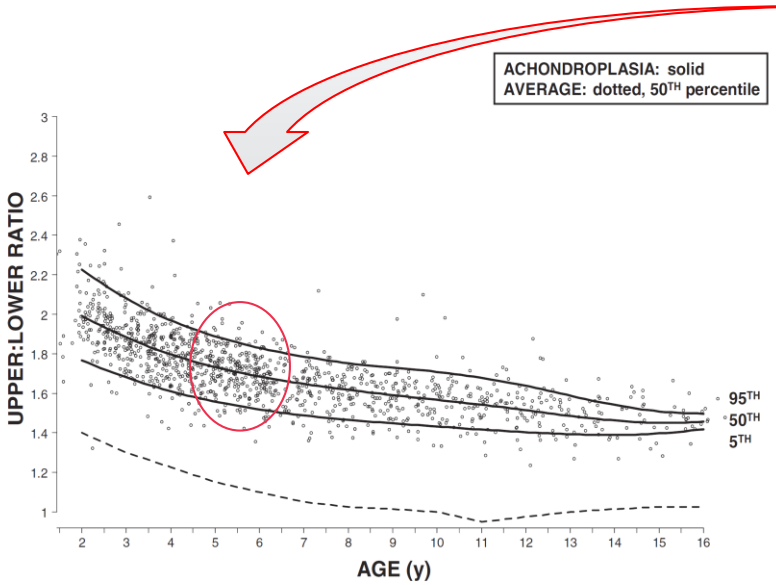
Lower segment - Extremities

Horton W. et. al. The Journal of Pediatrics, 1978

Growth of the extremities is limited relative to normal growth of the trunk in achondroplasia

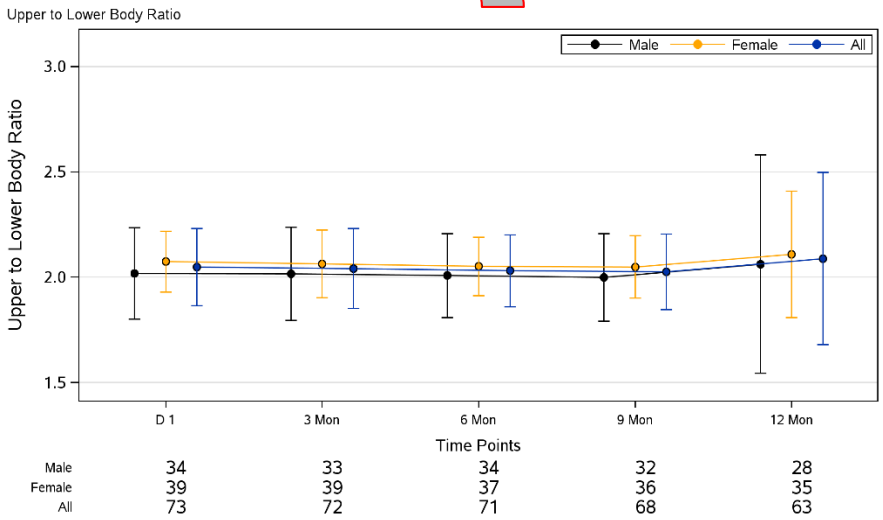
Disproportionate Growth is a Feature of Achondroplasia

Upper: Lower Body Segment Ratio
Published Reference Data



Hoover-Fong J. e al, *Am J Clin Nutr 2008*

Upper: Lower Body Segment Ratio
Data from 901(Baseline Growth and Natural History) Study



In assessing growth in achondroplasia, it is important to assess effects on body proportions

Baseline Growth and Natural History Study (BMN 111-901)

Past Medical and Achondroplasia-Related History

Preferred Term	Overall Population (N=74, %)
Otitis Media	38 (51.4%)
Congenital Bowing of Long Bones	33 (44.6%)
Sleep Apnea Syndrome	30 (40.5%)
Pain in extremity	18 (24.3%)
Deafness	16 (21.6%)
Speech Disorder Development	15 (20.3%)
Kyphosis	9 (12.2%)
Lordosis	9 (12.2%)
Hydrocephalus	6 (8.1%)
Foramen Magnum Stenosis	3 (4.1%)

Baseline Growth and Natural History Study (BMN 111-901)

Surgical and Medical Procedures

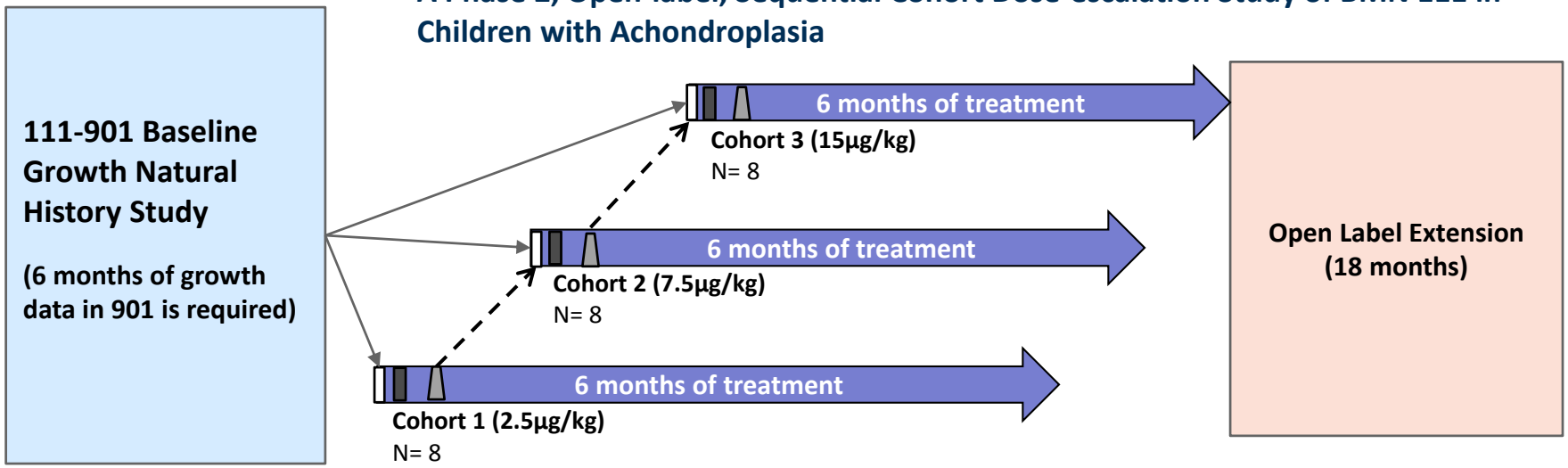
Surgical and Medical Procedures	Overall Population (N=74, %)
Ear Tube Insertion	42 (56.8%)
Adenotonsillectomy	39 (52.7%)
Spinal Decompression	13 (17.6%)
Ventriculo-peritoneal shunt	4 (5.4%)

BMN 111-202

A Phase 2, Open-label, Sequential Cohort Dose-Escalation Study of BMN 111 in Children with Achondroplasia

BMN 111-202 Study Design

A Phase 2, Open-label, Sequential Cohort Dose-escalation Study of BMN 111 in Children with Achondroplasia



Primary objective:

Evaluate the safety and tolerability of daily SC injections of BMN 111

Secondary objectives:

Evaluate change from baseline in annualized growth velocity, growth parameters, and body proportions following daily SC injections of BMN 111

To evaluate PK profile of BMN-111 in children with achondroplasia

- Subjects with achondroplasia age 5-14 who completed 6 months in Baseline Growth Natural history study (BMN 111-901) and have baseline growth velocity data are enrolled in BMN-111 -202 study
- Safety data is regularly reviewed by the independent Data Monitoring Committee (DMC)
- Subjects who completed 6 months of treatment in protocol 202 have an option to continue BMN-111 in the extension

BMN 111-202 Study: Enrollment of 3 Cohorts Completed

- First subject enrolled in January of 2014
- Protocol amended to allow subjects who completed 6 months to take part in the 18-months extension
- During 2014, the DMC regularly reviewed the data and provided recommendations to BioMarin on dose escalation to the next cohort
  - Based on DMC recommendations, BioMarin enrolled patients in cohorts 1 (2.5µg/kg), 2 (7.5µg/kg), and 3 (15µg/kg) according to the protocol
- BioMarin will report 6-month data for 3 cohorts in 2Q 2015
- Safety data (as it becomes available) and regulatory input will determine whether additional doses can be explored

BioMarin completed enrollment of all 3 cohorts of BMN 111-202 study in November of 2014

Rationale for Interest in Study in Younger Children with Achondroplasia

- Infants and toddlers with ACH are at risk for significant medical complications
- BMN-111 may provide greater benefit when started at a younger age
  - Initiation of BMN-111 at a younger age has the potential to improve growth and other complications of achondroplasia
- BioMarin is working on a protocol to explore effects of BMN-111 in younger children

BIOMARIN





Cathleen Raggio, M.D.
Attending Orthopedic Surgeon,
Co-Director, The Kathryn O. and Alan C. Greenberg
Center for Skeletal Dysplasias
Hospital for Special Surgery, New York

BIOMARIN ANALYST AND INVESTOR DAY 2014

Achondroplasia

Cathleen L. Raggio MD
Orthopedic Director K.O. and A.C. Greenberg Center
for Skeletal Dysplasias-Hospital for Special Surgery

Achondroplasia

- What is it
- What do the patient/parents need to be aware of as they grow-the medical roadmap
- Patient stories

Achondroplasia

- Most common form of non-lethal skeletal dysplasia
- 1 case per 25,000 births
- Autosomal dominant inheritance pattern
- Single gene, **AD trait** (4p16.3)

  (gene coding for fibroblast growth factor receptor 3)

- Advanced paternal age
- Intelligence is normal
- Abnormal endochondral bone formation is primary defect



Molecular Pathogenetic Breakdown

- *FGFR3* chromosomal locus 4p16.3
  - Autosomal Dominant
  - Over 80% of affected individuals are born to average stature parents-random new mutation
  - >99 % of individuals with Achondroplasia have one of two mutations in FGFR3 resulting in Gly380Arg:
    - 98% G>A point mutation at nucleotide 1138
    - 1% G>C point mutation at nucleotide 1138



Fig 1. Caso 1 - Feto com membros curtos e encurvados,
cefalia, tórax estreito com hipoplasia pulmonar e a
protuberante

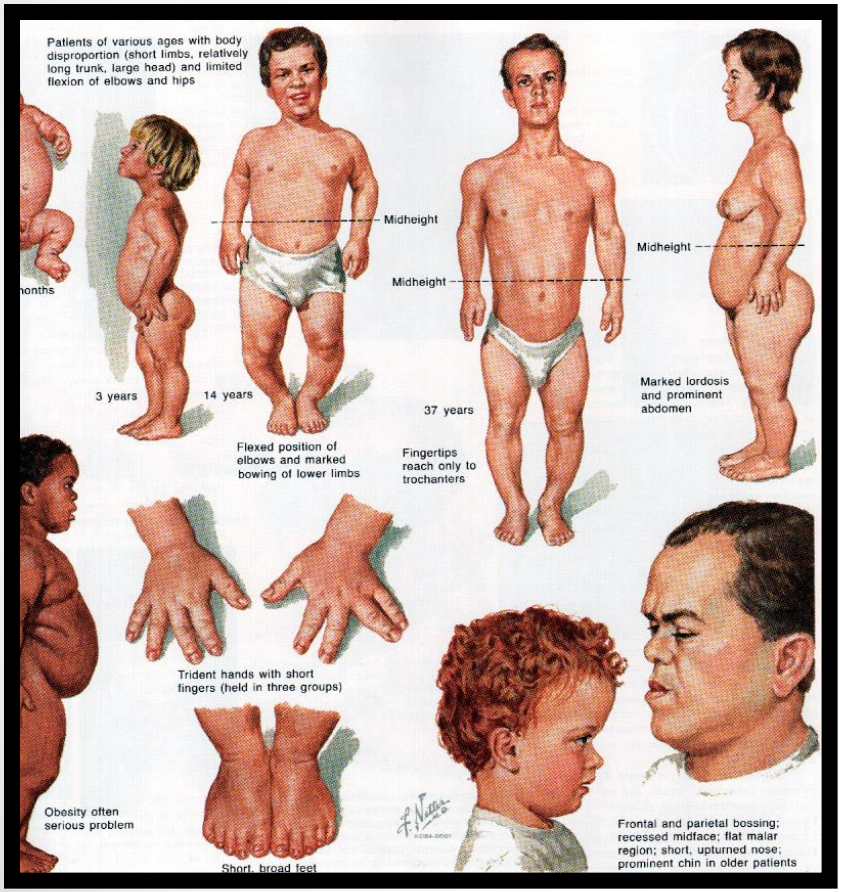








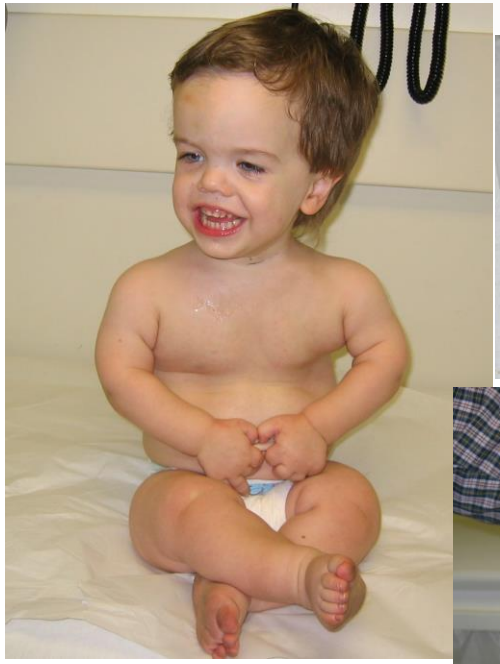
Achondroplasia Clinical General



- **<u>Limbs</u>**: rhizomelic shortening recognized at birth, elbow and hip flexion contractures, radial head dislocations, genu varum, waddling gait, hypotonia
- Relatively long, narrow trunk

Clinical Features

- Short stature
- Rhizomelic shortening of the arms and folds on limbs
- Limitation of elbow extension
- Trident configuration of the hand
- Genu Varum
- Exaggerated lumbar lordosis
- Spinal stenosis
  - ***FORAMEN MAGNUM***
- Large head with frontal bossing
- Most have hydrocephalus-usually communicating
- Midface hypoplasia



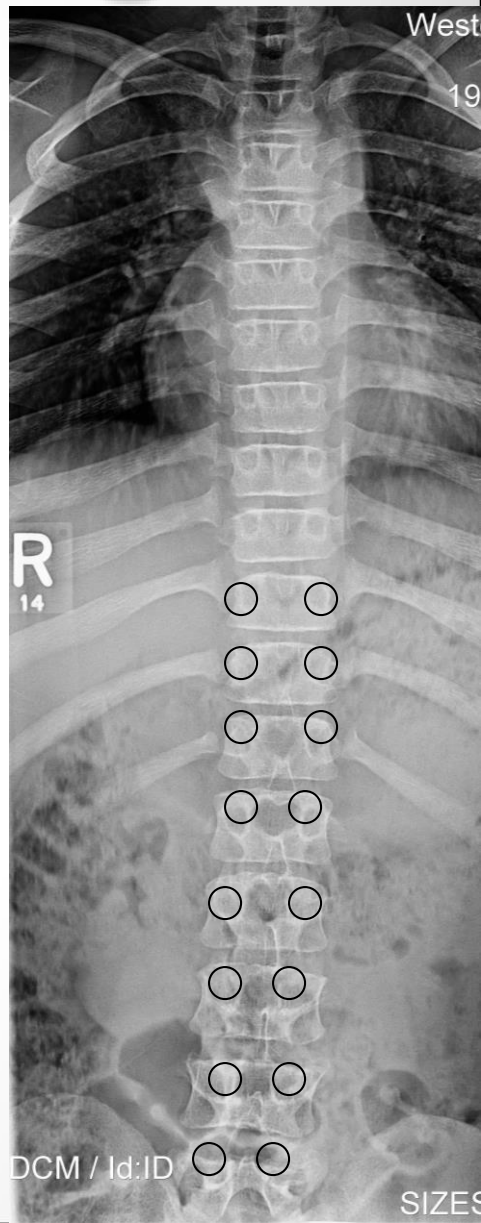




Radiographic findings

- Metaphyseal dysplasia
- Narrowing of the interpediculate distance of the spine
- Notch-like sacroiliac groove
- Genu varum and ankle varum with relative overgrowth of fibula
-





Achondroplasia- The Medical Roadmap

- Age birth -2 : Foramen Magnum Stenosis; Thoracolumbar Kyphosis; Hypotonia
- Age 2-4:ENT-tonsils /adenoids; OM
- Age4-8: Social skills/Schooling – adjusting to “average”
- Age 8: Bowing /Instability of Knees; Limb Lengthening
- Teens and beyond: Spinal Stenosis

Achondroplasia Orthopedic Concerns

- *Spinal stenosis*
  - *Foramen Magnum*
  - *Cervical*
  - *Lumbar*
- *Thoracolumbar kyphosis*
- *Varus deformities of the knees*

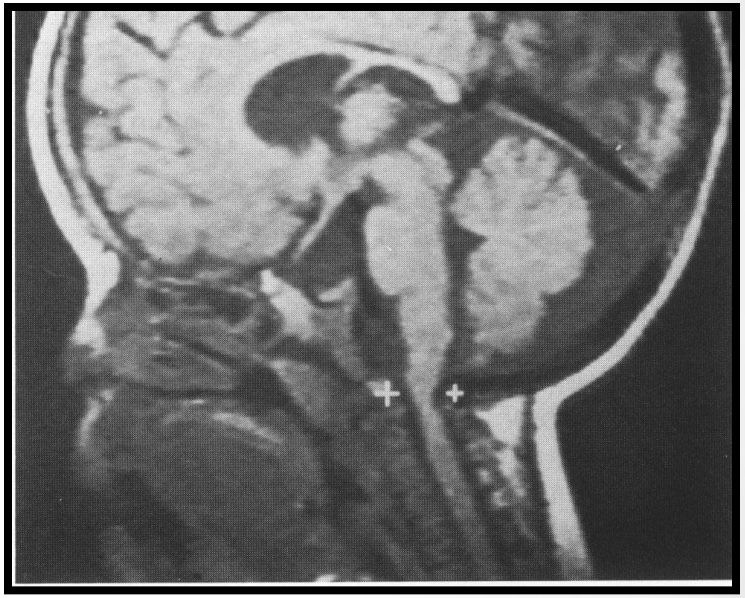
Achondroplasia

- **Diminished size of the foramen magnum**
- May result in a variety of neurologic problems

  (i.e.. cervicomedullary compression, apnea, death)

Delayed milestones ;handedness; snoring;

Too floppy



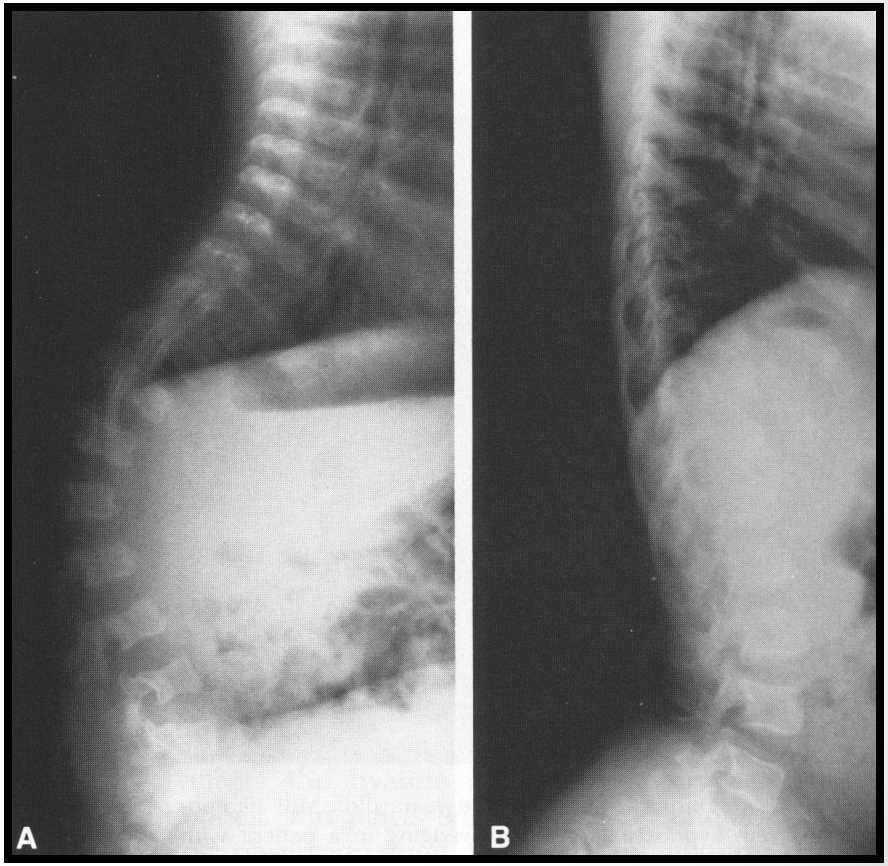


The Foramen Magnum Stenosis

- Work-up: MRI; Cervical spine xrays –flexion – extension
- Sleep Studies
- Surgical Decompressions-50% we think!

Achondroplasia - Kyphosis

- Thoraco-Lumbar Kyphosis is present before walking age but generally improves with ambulation



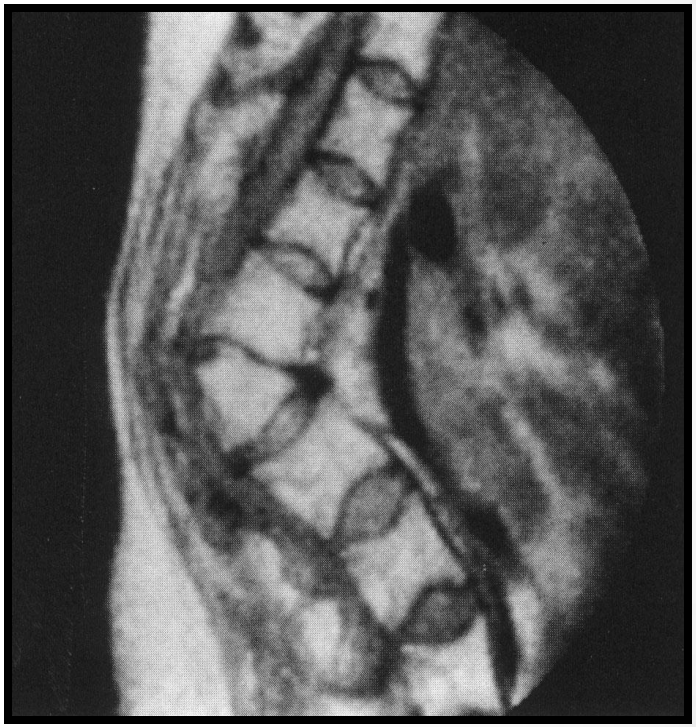
Achondroplasia - Kyphosis

- Resolves in 90% of cases:
  - observe prior to ambulation
- If No resolution after ambulation
  - Brace
- Candidates for surgery
    - persistent apical wedging
    - kyphosis > 40 degrees after age 5


OUT OF BRACE
LEFT

Achondroplasia – Kyphosis-Adult

- Thoracolumbar Kyphosis
  - up to 35% incidence
- Kyphosis may be associated with apical wedging at T12 or L1



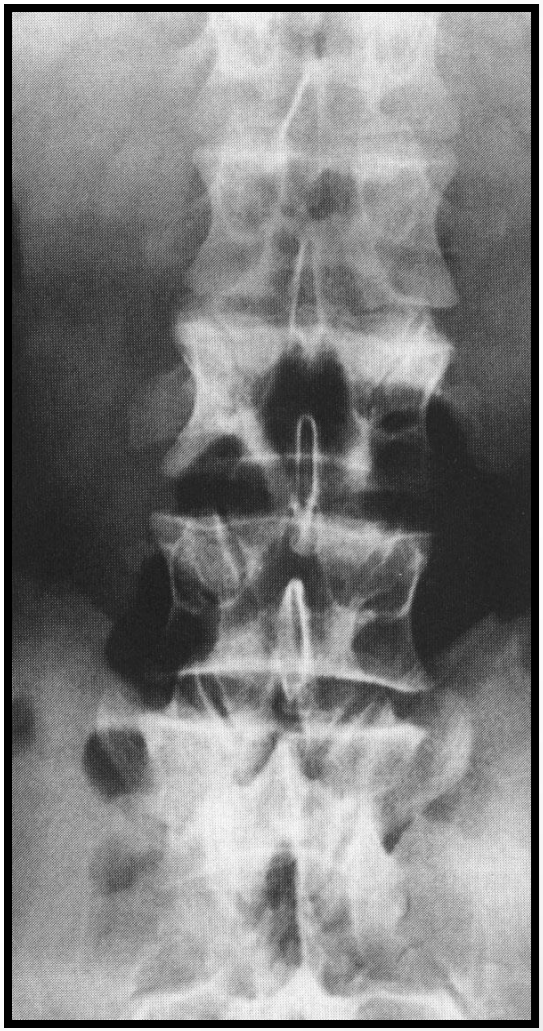
Kyphosis -Adults

- What happens?

- Loss of bladder/ bowel control
- Spasticity
- Loss of walking ability
- Pain

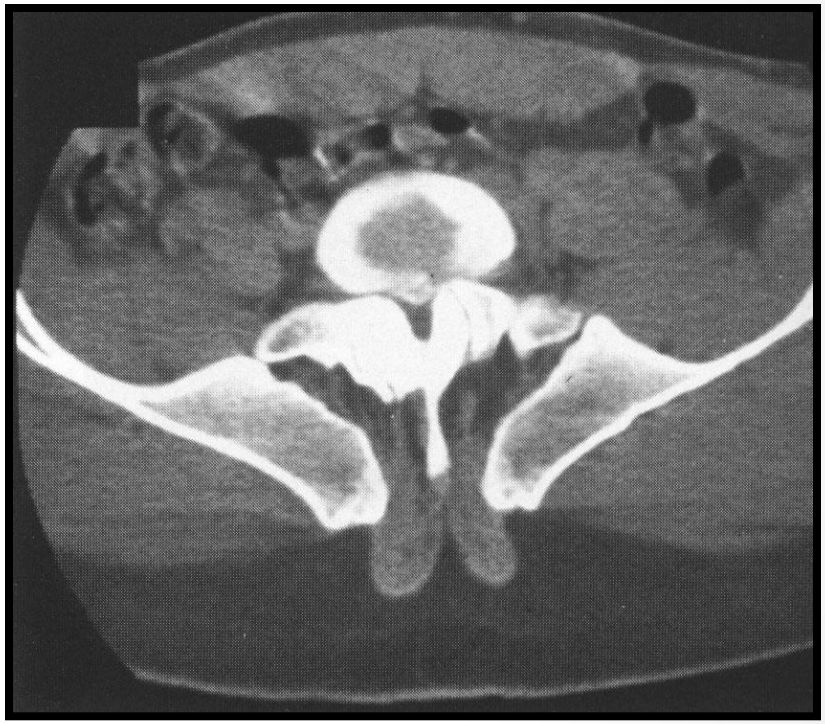
Achondroplasia - Stenosis

- Short, thickened pedicles
- Interpedicular narrowing



Achondroplasia - Spine

- Spinal stenosis
  - >50%
- Thickened laminae
- Thickened facets
- **Short, thickened pedicles**
- **Interpedicular narrowing**



Achondroplasia – Stenosis SYMPTOMS

- **Lumbar Stenosis**
  - usually occur in late adolescence through early adult-hood
  - posterior decompression without fusion
- **Cervical Stenosis**
  - usually occur in early to middle adult years
  - Decompression
  - 80-90% of our patients require one or both

Cervical Stenosis

- What happens?

- Loss of hand use
- Spasticity
- Difficulty walking
- Bowel/bladder changes
- Paralysis


SAG T2 F/S
FoV: 220 mm
Slice: 3 mm
BW: 122.0703125
C: 398.0 W: 797.0
P
Series: 4
Image no: 9
Image 9 of 18
F
Coil: CS12

Lumbar Stenosis

- What happens?

- Decreased ability to walk
- Pain
- Numbness

ADULT-LUMBAR



ADULT-LUMBAR



ADULT-LUMBAR



Achondroplasia - Genu Varum

- Genu Varum (second major concern)
  - affects at least 50%
- Etiology
  - more rapid growth of fibula postulated
    - (intramembranous growth)
- OA is rare

Achondroplasia - Genu Varum

- Genu varum
  - Two treatments
    - proximal Tib-Fib osteotomy
    - proximal or distal fibular epiphysiodesis
  - Bracing is NOT effective
  - INDICATION for SURGERY- PAIN and THRUST /Instability

Management-SUMMARY

- Narrowing of the foramen magnum.
  - X-rays: C-spine with flexion/extension views
  - MRI
  - Surgical decompression
- Thoracolumbar kyphosis
  - Supportive strollers, carrying devices, etc.
  - Bracing if necessary, some patients come to surgery
- Genu varum (bowed knees)/instability-surgery
- Lumbar lordosis
- Spinal stenosis
  - Surgical decompression with fusion

Short limbs - Lengthening Surgery

Achondroplasia- Interventions

- General Good health managements –weight control; routine exercises
- Surgery

- The question is : Is there a way to affect the bone dysplasia such that the need for surgical intervention would be lessened?
- This would result not only in a paradigm shift in the treatment but MORE importantly a Quality of Life shift for the people.

Patient Stories

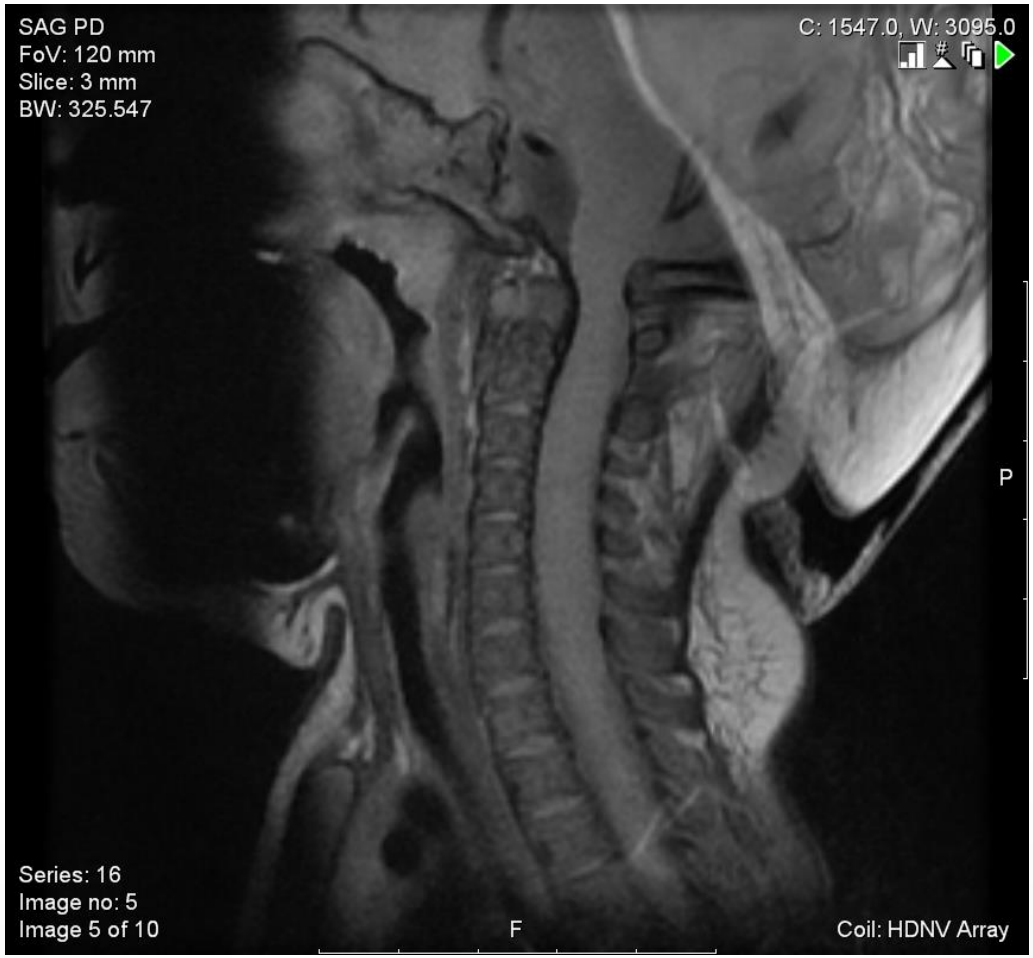
- Baby with foramen magnum stenosis- surgery needed
- Baby with FM stenosis- no surgery – flaccid paralysis




LEFT
CROSS TAB


LEFT
AP
SUPINE

BABY


SAG PD
FoV: 120 mm
Slice: 3 mm
BW: 325.547
C: 1547.0, W: 3095.0
P
Series: 16
Image no: 5
Image 5 of 10
F
Coil: HDNV Array

BABY BRAIN


LOC
FoV: 300 mm
Slice: 10 mm
BW: 122.07
C: 407.0, W: 815.0
P
Series: 1
Image no: 5
Image 5 of 11
F
Coil: HDNV Head

Achondroplasia- Interventions

- General Good health managements –weight control; routine exercises
- Surgery

- The question is : Is there a way to affect the bone dysplasia such that the need for surgical intervention would be lessened?
- This would result not only in a paradigm shift in the treatment but MORE importantly a Quality of Life shift for the people.

THANK YOU



Q&A



BMN 250 FOR MPS IIIB AND BMN 190 FOR CLN2, LATE INFANTILE FORM OF BATTEN DISEASE

BIOMARIN ANALYST AND INVESTOR DAY 2014

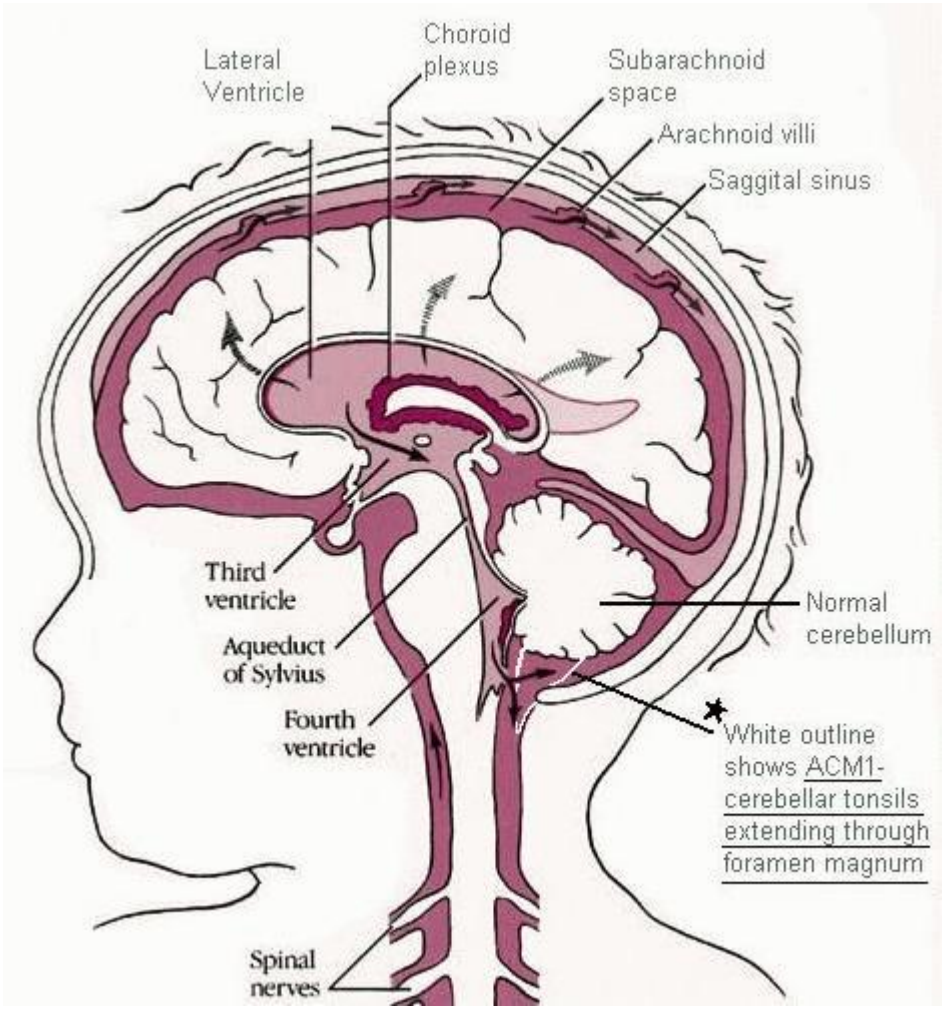
Dave Jacoby, M.D., PhD, Senior Group Medical Director
BioMarin

Platform for CNS-delivery of ERT for the Pediatric Neurodegenerative LSDs

- Programs in CLN2 (late infantile form of Batten disease) and MPS IIIB (Sanfillipo B disease)
- Predominantly neurological presentation, currently no form of treatment. Barriers to development have been access to CNS and distribution to all affected cells in the brain and spinal cord
- Technical advances for neuro-predominant LSDs:
  - Direct delivery to CNS by infusion into central CSF structures using intraventricular reservoirs
  - Engineered proteins (BMN 250) to maximize cell uptake and cross-correction

Clinically enabling studies suggest widespread distribution in CNS and correction of metabolic defects

CSF Flow: Rationale for ICV Delivery

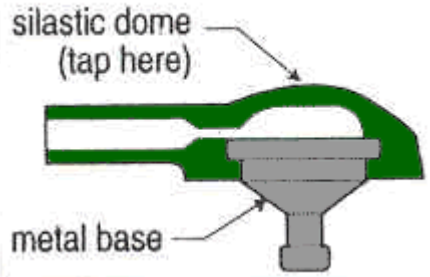


Why Ventricular Delivery?

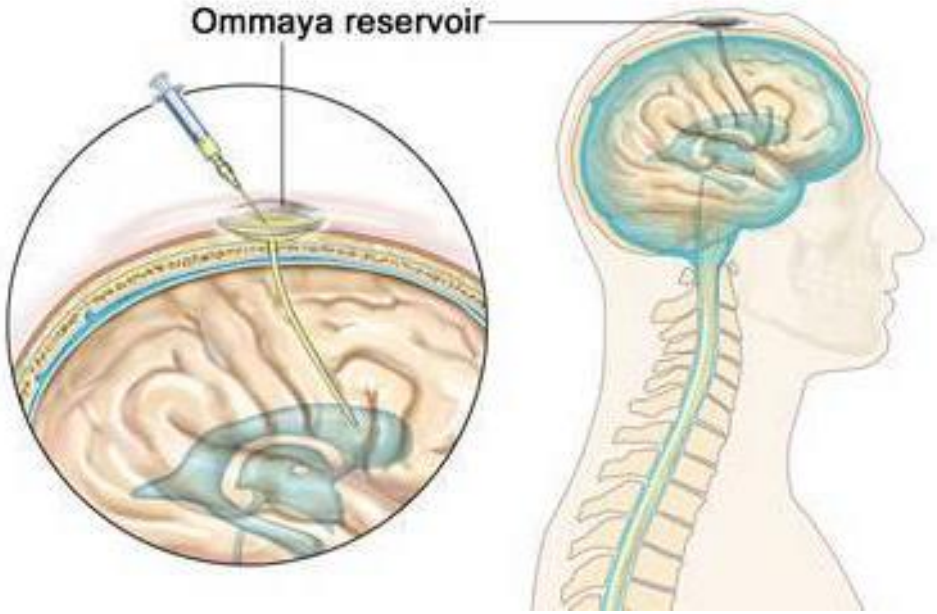
- BBB necessitates central access
- Delivery at source of CSF
- Flow to all parts of CNS
- Permeates through neuropil
- Approved devices, safe in children
- Approved for medical therapy

Ventricular Reservoirs for Drug Administration

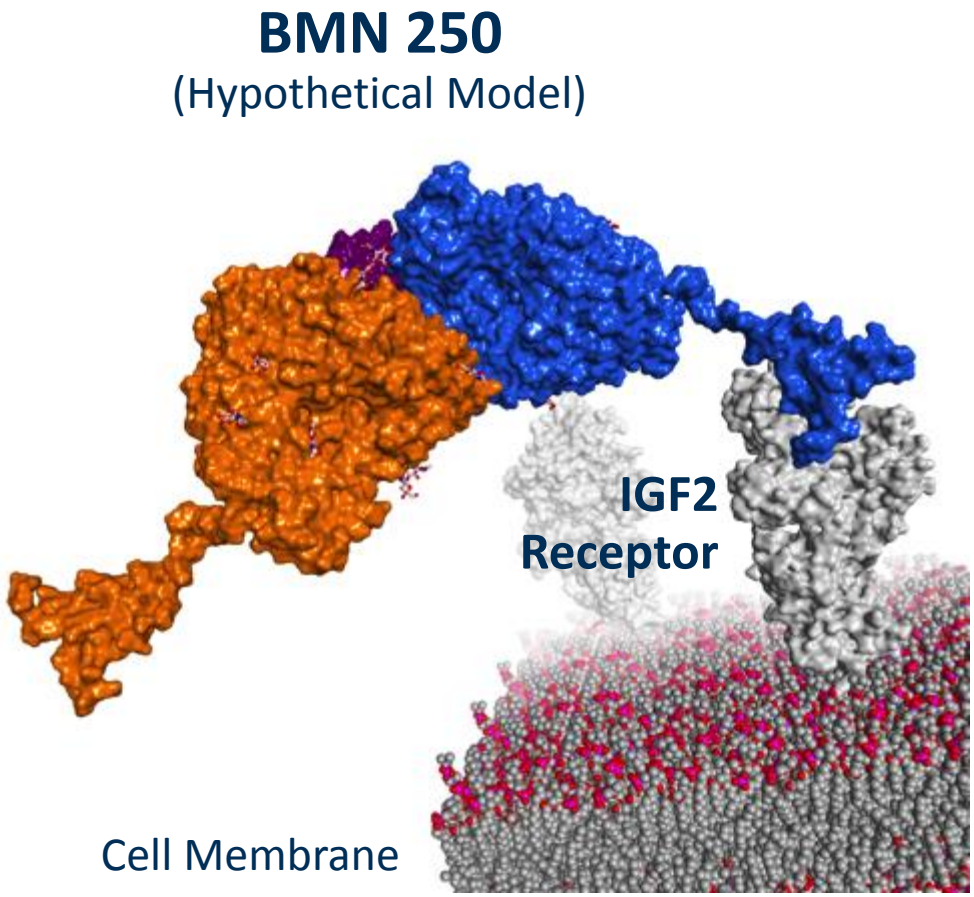
- **Permanently in-dwelling subcutaneous port**
- **Base plate seal with skull burr-hole**
- **Fine catheter communicates between port and a lateral ventricle**
- **May remain several years before revision**



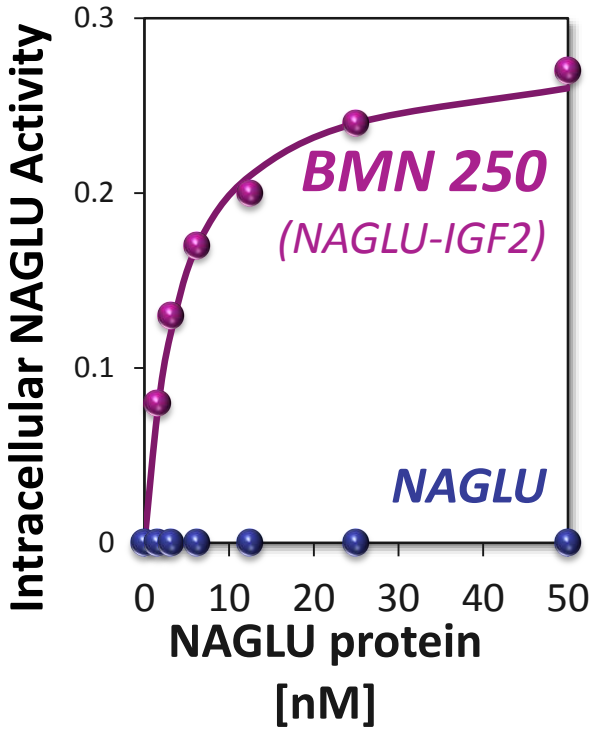




NAGLU is linked to IGF2 (or "GILT") tag for cell receptor-mediated uptake and delivery to lysosomes

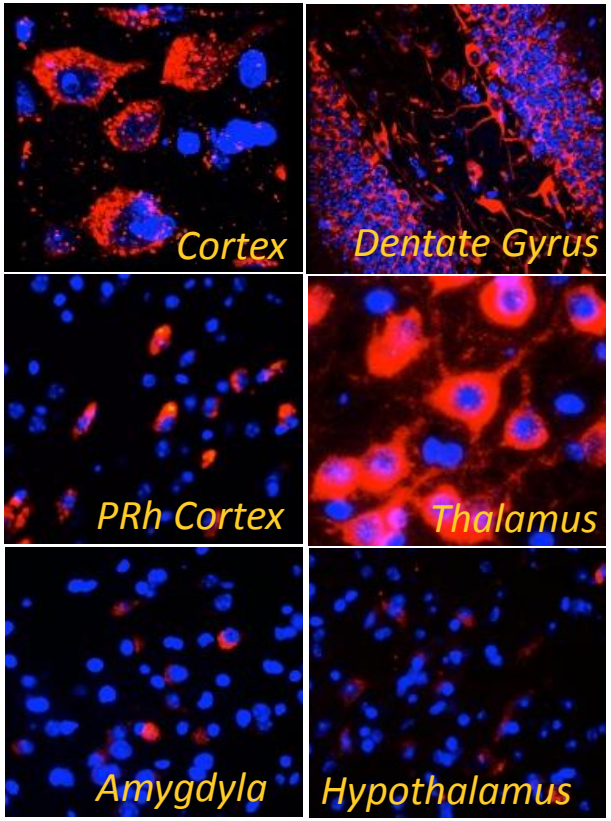


2V5P.pdb



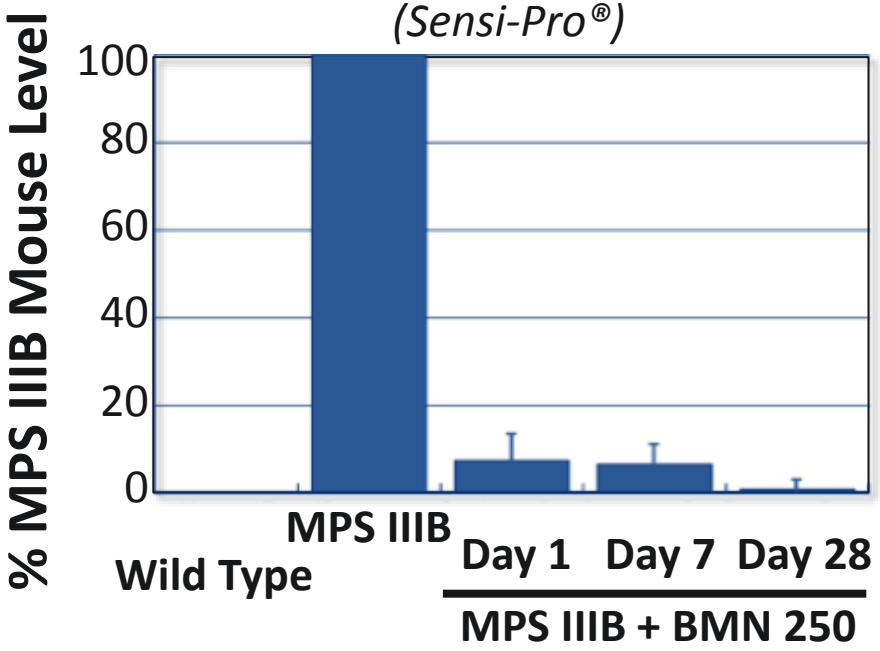
BMN 250 treatment results in broad distribution & clearance of accumulated heparan sulfate in MPS IIIB mouse brain

NAGLU & ***Cell Nuclei***
in MPS IIIB mouse brain





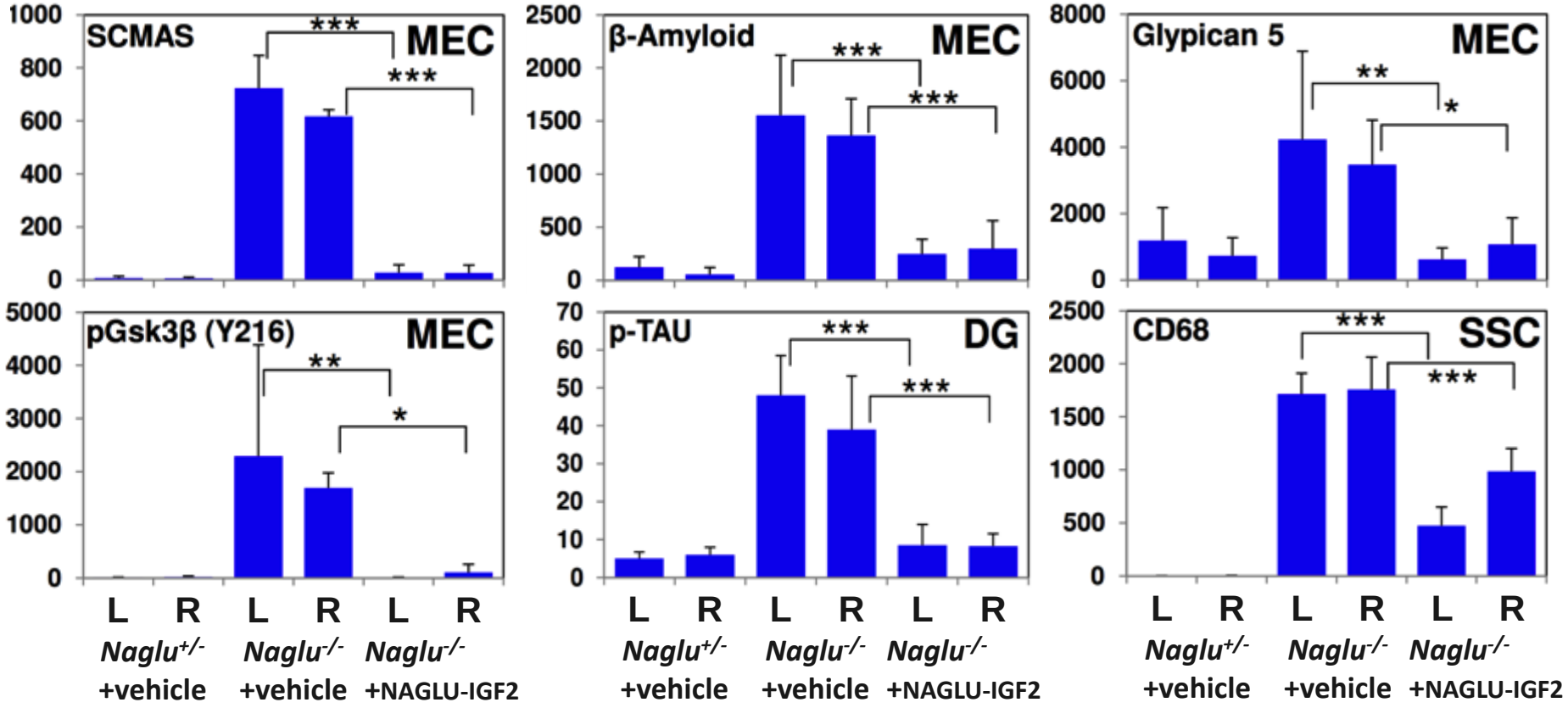
Lysosomal Heparan Sulfate
(Sensi-Pro®)



100 µg x 4 ICV doses over 2 weeks
1, 7 & 28 days post last dose

NAGLU-IGF2 treatment results in reduction of pathological biomarkers in model MPSIIIB brains

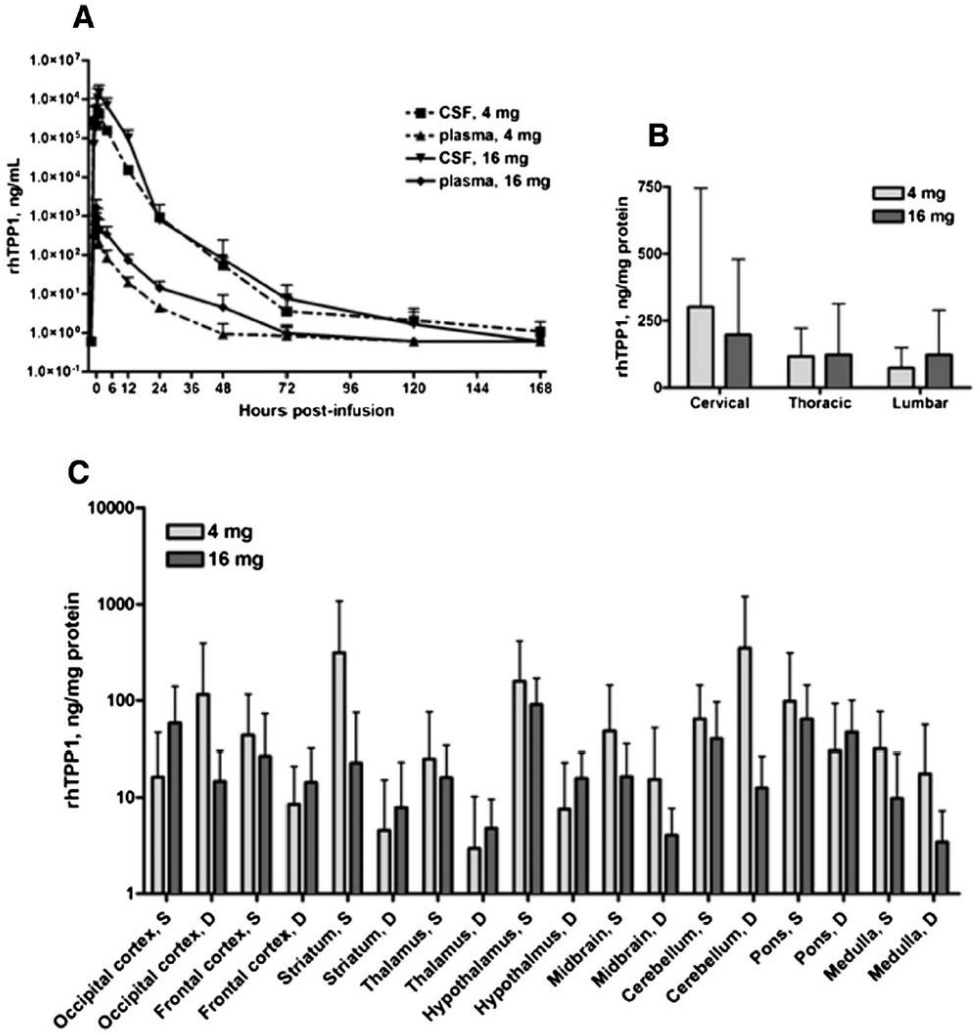
Kan, S.-h. et al. PNAS 111(41):14871. 2014



L, R = left, right = ipsilateral, contralateral

MEC = medial entorhinal cortex; DG = dentate gyrus; SSC= somatosensory cortex

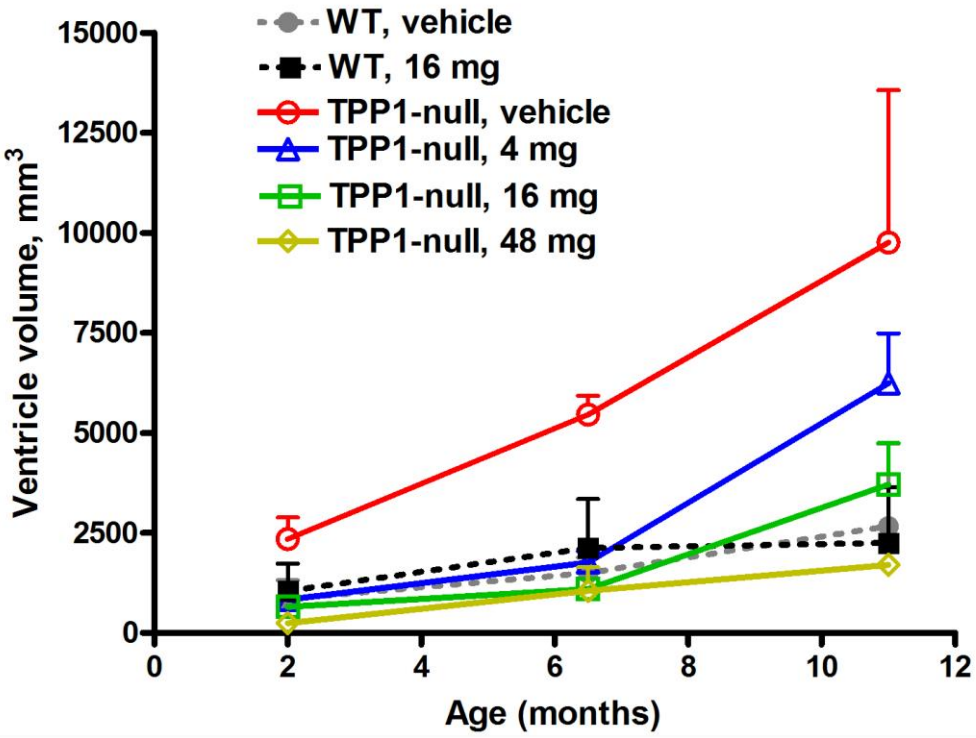
Widespread Biodistribution of rhTPP1 in Large Animal Model of CLN2

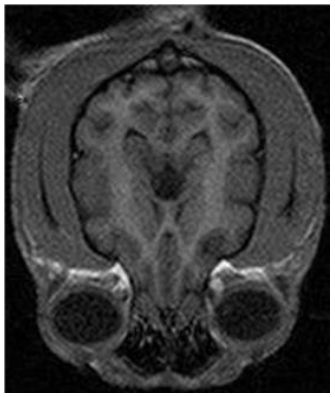


- ICV administration shows 3 log greater exposure in CSF > plasma
- Levels above uptake threshold for >48 hours after administration
- Cellular half-life about 9 days

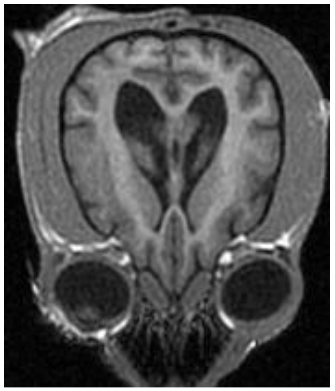
- Widespread distribution of rhTPP1 throughout neuroaxis
- Superior to lumbar IT dosing
- Vuillemenot et al., 2014

rhTPP1 Attenuates Brain Atrophy in Dog Model of CLN2





4 mg TPP1

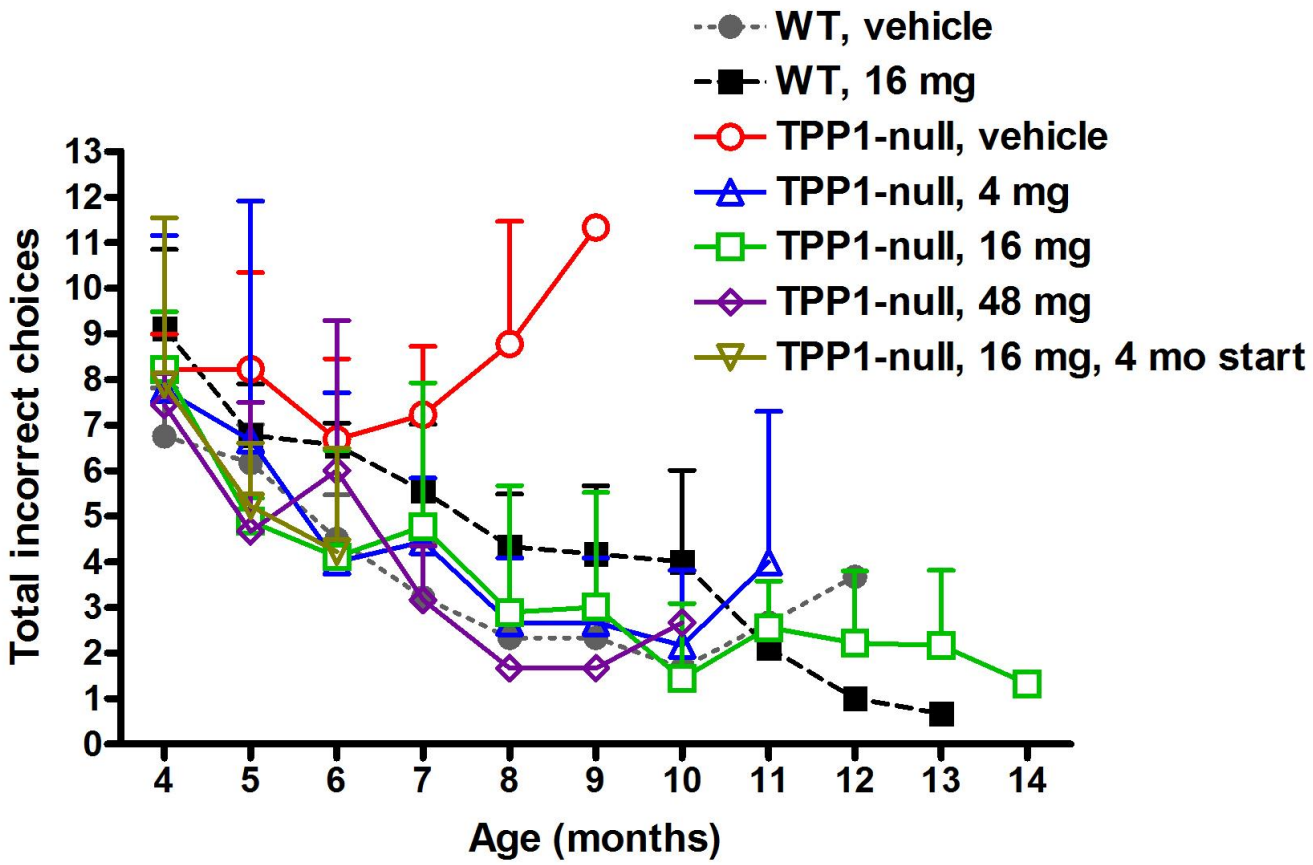


vehicle

- Cerebral atrophy hallmark of both CLN2 and MPSIIIB diseases
- Atrophy measured by brain MRI is recapitulated in a dog model of CLN
- Attenuation of atrophy occurs with ICV rhTPP1 treatment of dogs
- Prevention of atrophy noted at higher doses

Katz et al., 2014

rhTPP1 Abrogates Dementia in Dog Model of CLN2



- CLN2 dog loses object memory with disease as tested by a simple T-maze
- Treated dogs retain cognitive function over long study period

Katz et al., 2014

BMN 190-201 Study Update

- Study will be fully enrolled DEC/2014
  - Last patient completed DEC/2015
- Clinical sites: Hamburg, Rome, London and Columbus, Ohio
- All patients tolerating therapeutic dose (300 mg qow)
  - > 150 infusions performed in 21 patients currently
  - Up to 30 infusions completed in a single patient
  - No complications with ICV device for any patient
  - Well tolerated dosing in all patients
- Primary readout will be quantitative clinical assessment supported by brain MRI

BIOMARIN



BMN190: rhTPP1 Direct Enzyme Replacement for the Treatment of CLN2 Disease

Alfried Kohlschuetter, M.D.

Stop Childhood Dementia

A Deadly Disease in the Young as a Model for Fighting a Plague of the Elderly



Alfried Kohlschütter, MD
Professor of Pediatrics
University Medical Center Eppendorf, Hamburg, Germany

New York NY, December 10, 2014

What are we talking about?

(1) Dementia in childhood is an important reality

(2) How is the evolution of childhood dementia over time?

(3) Can the progression to dementia be stopped?

Why study rare forms of dementia in the young?

Dementia in elderly persons

- Many causes (genetics, arteriosclerosis, diabetes, high blood pressure etc.)
- Disease mechanism(s) complex and difficult to study
- Development of therapies particularly difficult

Dementia in young persons

- One single cause
- Disease mechanism easier to study
- Basis for rational approach to treatment

Dementia in Young Persons

What is dementia?
Loss of cognition (≠ Mental Retardation)
Is dementia a reality for pediatricians?

Pediatric conditions causing dementia
Neuronal Ceroid Lipofuscinoses (NCL)
Mucopolysaccharidoses (MPS)
Niemann-Pick Disease type C
Adrenoleukodystrophy
Metachromatic Leukodystrophy
Krabbe Disease

NCL disorders
CLN1 Disease
CLN2 Disease
CLN3 Disease
CLN4 Disease
CLN5 Disease
CLN6 Disease
CLN7 Disease
CLN8 Disease
CLN9 Disease
CLN10 Disease
CLN11 Disease
CLN12 Disease
CLN13 Disease
CLN14 Disease

Neuronal Ceroid-Lipofuscinoses (NCL)

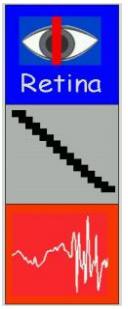
Most frequent group of disorders causing dementia in young persons. Many different diseases, but they have <u>in common</u>:

- **A clinical syndrome**

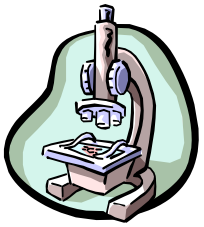
Loss of vision

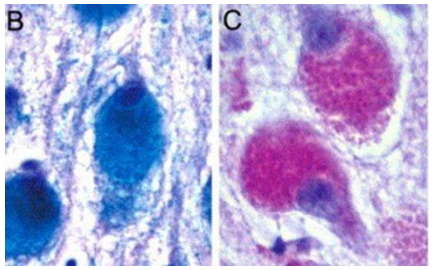
Dementia

Epilepsy

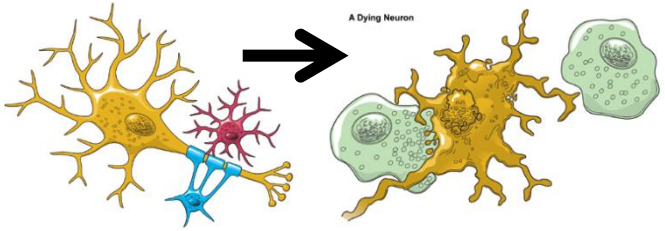


- **Storage of material in cells (ceroid-lipofuscin)**





- **Dying nerve cells (neurodegeneration)**



An NCL disorders that breaks out in early childhood is

CLN2 Disease

Other names:

TPP1 Deficiency

Classical late infantile NCL

Janský-Bielschowsky Disease

(„Batten Disease“)

The disease is caused by a genetic deficiency of an enzyme, tripeptidyl peptidase 1 (TPP1)

Patients with CLN2 Disease (TPP1 Deficiency)



CLN2 Disease

Gene product: Tripeptidyl peptidase 1 (TPP1)

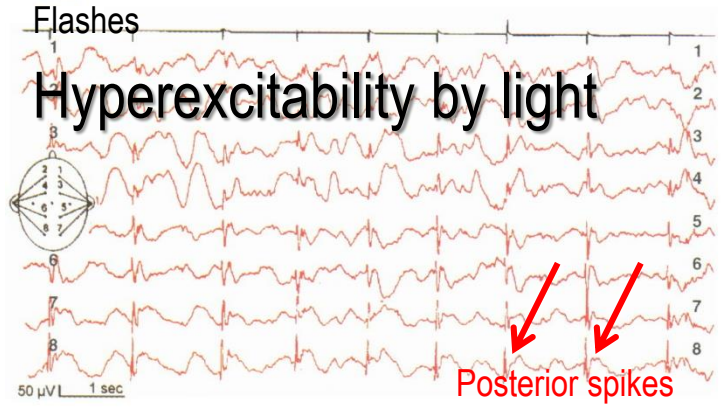
Patients are initially healthy.

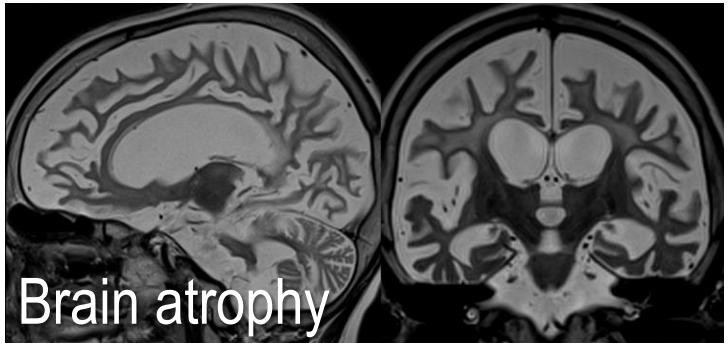
Disease starts with ~ 3 years

- **Epilepsy**
- **Developmental standstill**

  → **gradual loss of all mental and motor abilities**
- **Loss of vision**







How can we approach therapy in CLN2 Disease

This is an incurable, slowly progressive disease.

Suppose we have an idea for possible treatment.

How can we test and measure its efficacy?

We need quantitative data

- on the **clinical course over time** and
- on the **variability** of the course between individuals

Late Infantile Neuronal Ceroid Lipofuscinosis: Quantitative Description of the Clinical Course in Patients With *CLN2* Mutations

American Journal of Medical Genetics 112:347–354 (2002)

Robert Steinfeld,[1] Peter Heim,[2] Henning von Gregory,[1] Kerstin Meyer,[1] Kurt Ullrich,[1] Hans H. Goebel,[3] and Alfried Kohlschütter[1]*

Development of a **Clinical Scoring** that is disease-specific, robust, suitable for retrospective analysis and statistical evaluation

Function quantified	Scores used
Motor function	Normal = 3
Seizures	Abnormal = 2
Visual function	Poor = 1
Language	No function = 0

CLN2 Disease: Scoring of Motor and Language Function

Functional category	Performance	Score
Motor function	Walks normally[a]	3
	Frequent falls, clumsiness obvious	2
	No unaided walking or crawling only	1
	Immobile, mostly bedridden	0
Language	Normal (individual maximum)[b]	3
	Has become recognizably abnormal	2
	Hardly understandable	1
	Unintelligible or no language	0

Late Infantile Neuronal Ceroid Lipofuscinosis:
Quantitative Description of the Clinical Course in Patients With *CLN2* Mutations Steinfeld et al. Am J Med Genet 2002

CLN2 Disease

TPP1 Deficiency

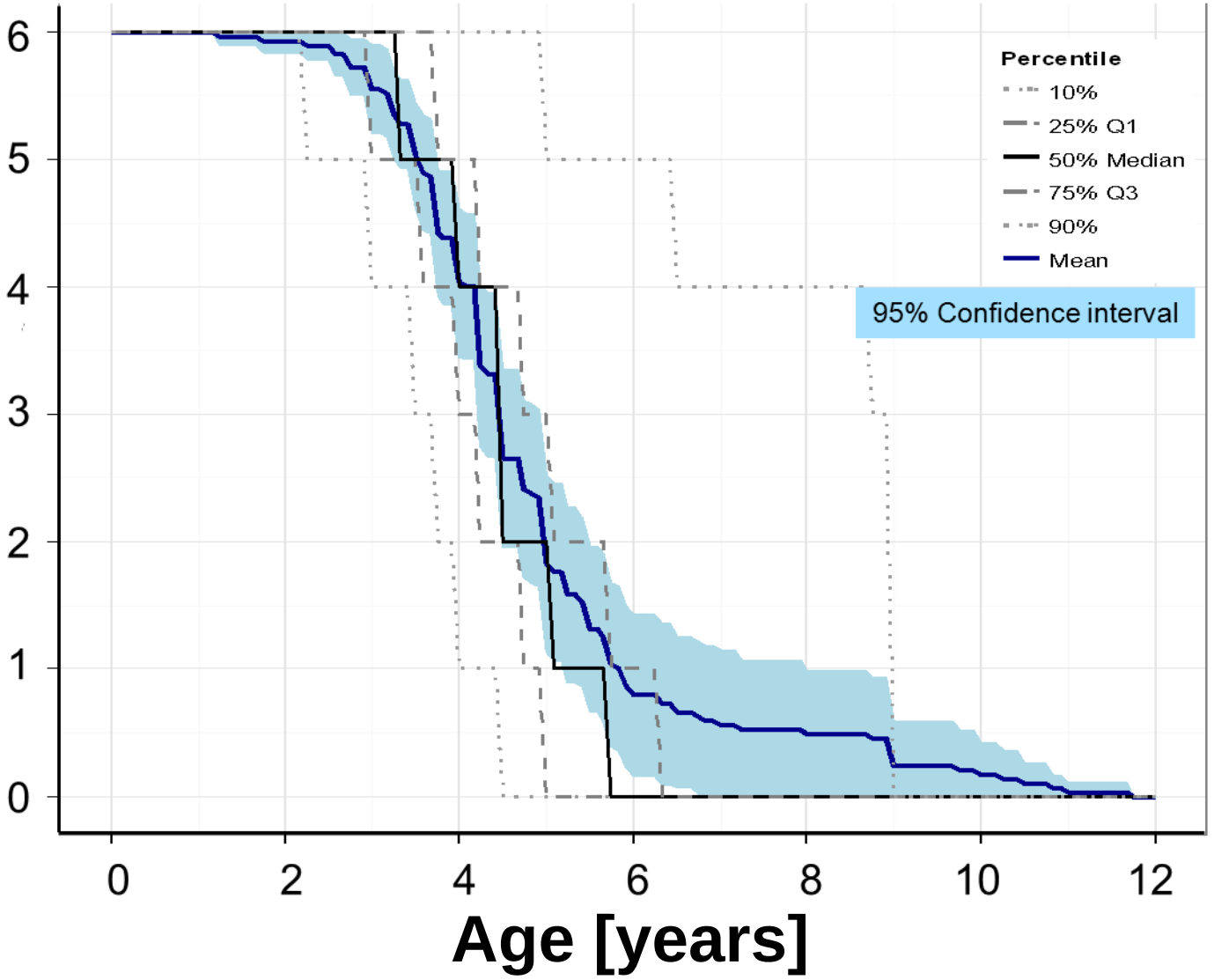
Natural clinical course of 62 patients

Clinical Score

Sum of WALKING and TALKING

Normal = 3
Abnormal = 2
Poor = 1
No function = 0

(Maximum = 6)





Man's better friends

in disease research



- Much research uses artificial mouse models of human disease
- Mice are rather different from humans
- Mice don‘t live enough to develop certain chronic diseases

Many dogs have epilepsy

A dachshund strain was shown to have CLN2 disease



= An animal model quite close to CLN2 disease in young children

CLN2 Disease

Data from Biomarin CA

Deficiency of tripeptidyl peptidase 1 (TPP1)

TPP1 Research has demonstrated a potential for a safe and efficacious therapy in CLN2 patients

Species	Study Purpose	Results
TPP1 knockout **mouse** model	Potential for efficacy in animal model	▪Disease attenuated ▪Survival extension
TPP1-null **dachshund** model 	Potential for efficacy and safety in animal model	▪Functional improvement ▪Survival extension ▪Enzyme in many areas of brain ▪Manageable inflammatory reaction
Beagle	Brain distribution pattern	▪Enzyme in many areas of brain
Monkey	Potential for safety and brain distribution pattern	▪Dosing well tolerated ▪Enzyme in many areas of brain ▪Manageable inflammatory reaction

CLN2 Disease

Deficiency of tripeptidyl peptidase1 (TPP1)

A dog with CLN2, age 11 months

After mock treatment, severe motor disturbances



Video obtained from Charles A. O'Neill, Biomarin

CLN2 Disease

Deficiency of tripeptidyl peptidase 1 (TPP1)

A different dog with CLN2, age 13 months
After **intrathecal enzyme replacement therapy,**
Motor performance remarkably better



Video obtained from Charles A. O'Neill, Biomarin

CLN2 Disease

Deficiency of tripeptidyl peptidase 1 (TPP1)

Enzyme Replacement Therapy (Biomarin)

Recombinant human form of TPP1.
TPP1 too large to cross blood-brain barrier. Must be brought close to brain.

CLN2 dogs



- Infusion into CSF (liquid surrounding the brain) results in high levels and widespread distribution of active enzyme in the brain
- Functional improvement of dog

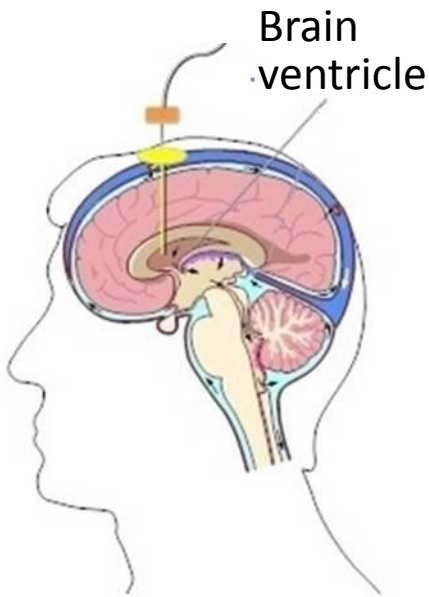


CLN2 children



Therapy trial phase I/II
in Hamburg
Started Sept 2013

Principal Investigator
Angela Schulz



CLN2 Disease

TPP1 Deficiency

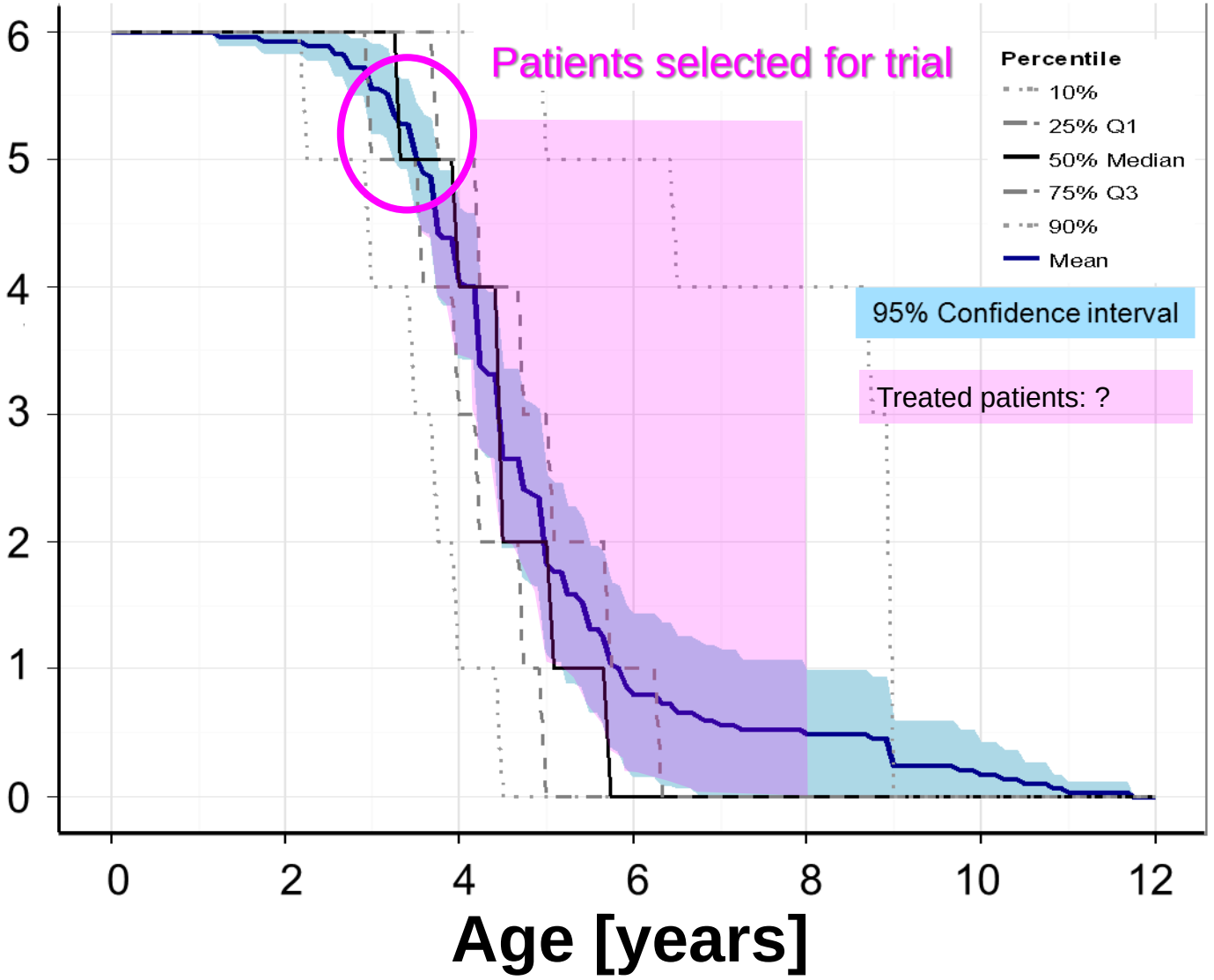
Using natural course data for evaluation of treatment

Clinical Score

Sum of WALKING and TALKING

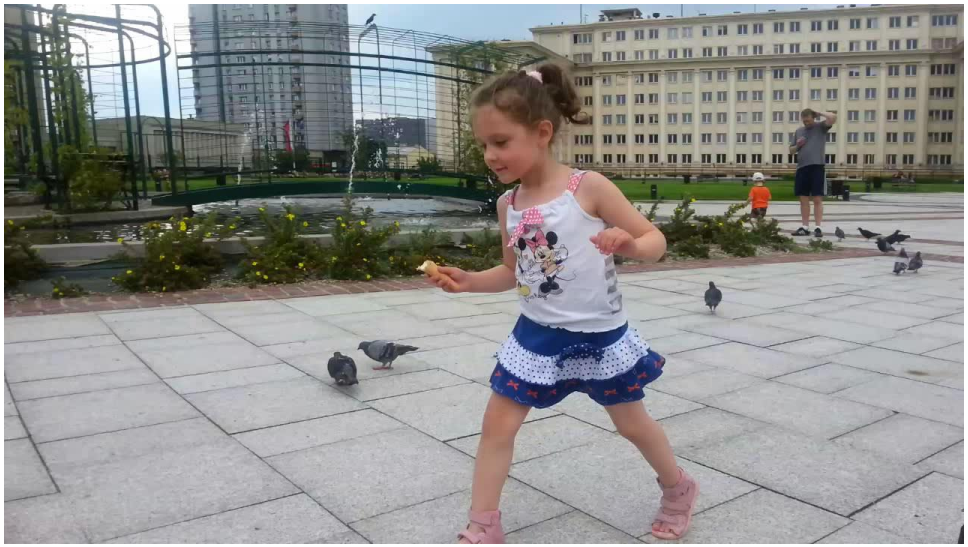
Normal = 3
Abnormal = 2
Poor = 1
No function = 0

(Maximum = 6)



CLN2 Disease

TPP1 Deficiency



A child early in the course:

Gait abnormal, but walks independently.

Trial inclusion possible



A child later in the course:

Independent gait lost.

Too late for treatment

CLN2 Disease

Phase I/II clinical trial with intraventricular TPP1 replacement therapy



Hamburg, November 2014



Technical functioning of application system and
tolerability of procedure: **Very good**

CLN2 Disease
and intraventricular TPP1 replacement therapy
Outlook

Functionality and Tolerance: Optimism warranted

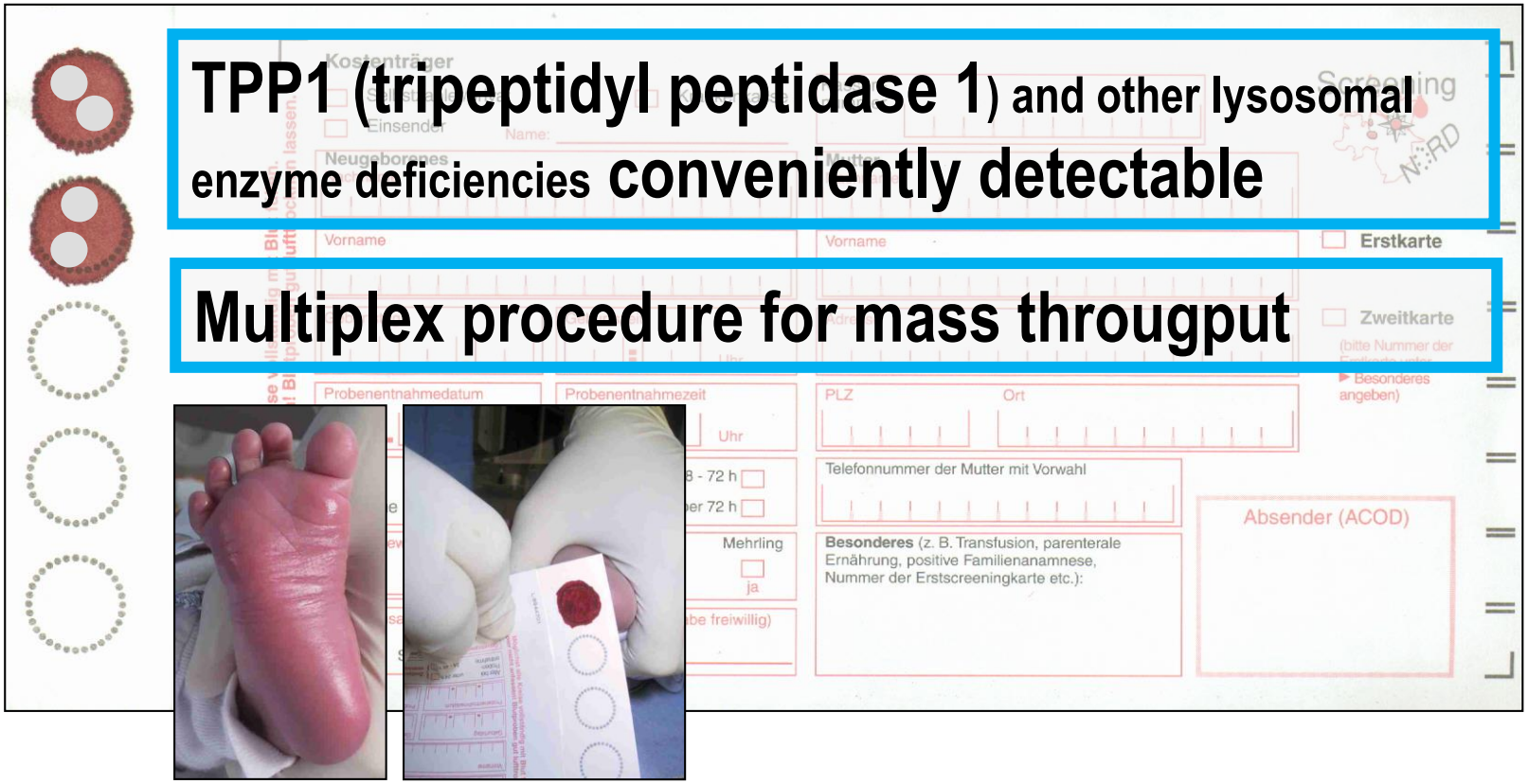
Efficacy:

if none:	Look for different approach
if moderate:	A door will have been opened Develop modifications
if good:	**Early diagnosis** is important Late talking infants are at risk Newborn screening ?

CLN2 Disease: Diagnosis in Dry Blood Spots



Filter paper method as used in newborn screening



Early diagnosis: prerequisite for effective treatment

Lukacs, Santavuori, Keil, Steinfeld, Kohlschütter. Clin Chem (2003)
Maeser, Iurascu, Cozma, Braulke, Schulz, Przybylski (in preparation 2014)

Universitätsklinikum Hamburg-Eppendorf

University Medical Center Hamburg Eppendorf
Child and Adolescent Medicine

Clinic for Degenerative Brain Diseases

CARE

AND

STUDY

Alfried Kohlschütter
Angela Schulz
Miriam Nickel
Annette Bley
Waltraud Hubert



Q&A



TALAZOPARIB (BMN 673) FOR MBRCA BC AND BMN 701 FOR POMPE DISEASE

BIOMARIN ANALYST AND INVESTOR DAY 2014

Len Post, Ph.D., Group Vice President, Chief Scientific Officer

Talazoparib (BMN 673): Registration program underway in BRCA carrier breast cancer

- EMBRACA Phase 3 study
  - BRCA carrier breast cancer patients
  - 2:1 randomization vs physician's choice chemotherapy
  - Sites open in 14 countries
  - Enrollment complete in 2H 2015

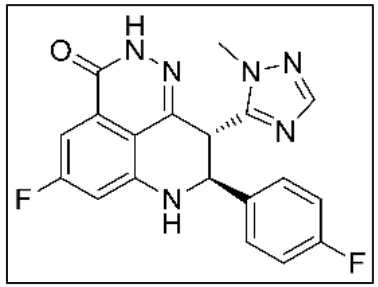
- ABRAZO Phase 2 study
  - BRCA carrier breast cancer patients
  - More than two prior chemotherapies, or prior platinum
  - Single arm study

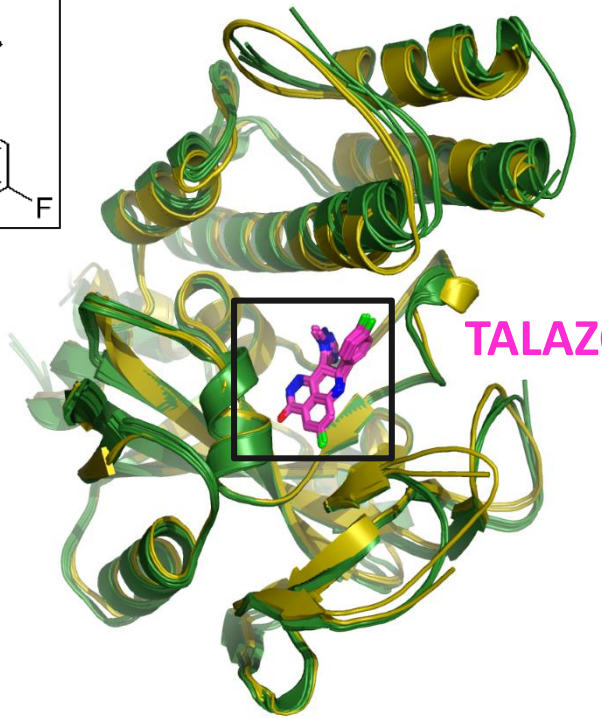
Talazoparib - Unique PARP inhibitor

- All clinical PARP inhibitors have low nM potency of inhibition of PARP catalytic activity.
- But talazoparib is 100x more potent than other PARP inhibitors in toxicity to sensitive tumor cells

- Explanation provided by J. Murai, Y. Pommier, and colleagues at NCI:
  - PARP inhibitors kill tumor cells by trapping a PARP-DNA complex that is toxic to cells with reduced ability to repair DNA damage.
  - Ability of PARP inhibitors to trap PARP-DNA complexes varies among PARP inhibitors with good catalytic inhibition.
  - Talazoparib traps PARP-DNA complexes with potency 100x greater than other clinical PARP inhibitors.

Compared to other PARP1 inhibitors that are directed toward sub-sites 1 and 2, **TALAZOPARIB** occupies a unique space within the extended NAD^+-binding pocket.





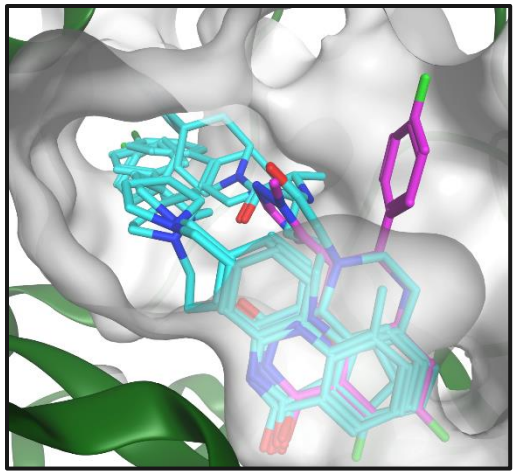
TALAZOPARIB

PARP1 catalytic domain

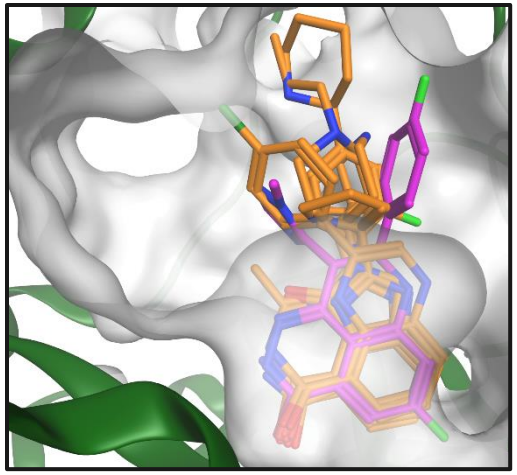
PARP2 catalytic domain

Aoyagi-Scharber et al Acta Crystallographica 2014

Sub-site 1



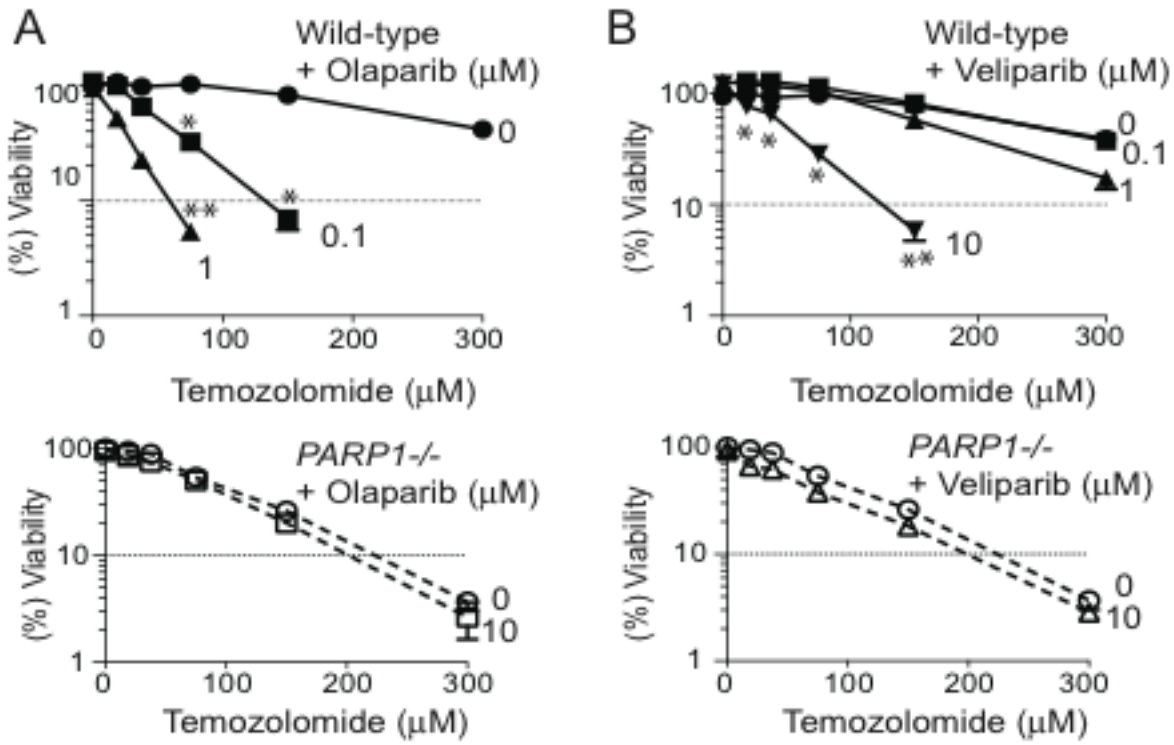
Sub-site 2



The question we get is : Why does trapping potency matter?

- Highly selective single agent activity, less potential off target activity
  - Deletion of PARP eliminates talazoparib cytotoxicity
  - Large range of separation between inhibition of sensitive and resistant cells
- Clinical dose of talazoparib is 1 mg once daily
  - Other PARP inhibitors are all hundreds of mgs qd or bid
  - Lower dose provides consistent PK and sustained inhibition of PARP
- PARP-DNA trapping is involved with synergy with some particular cytotoxics

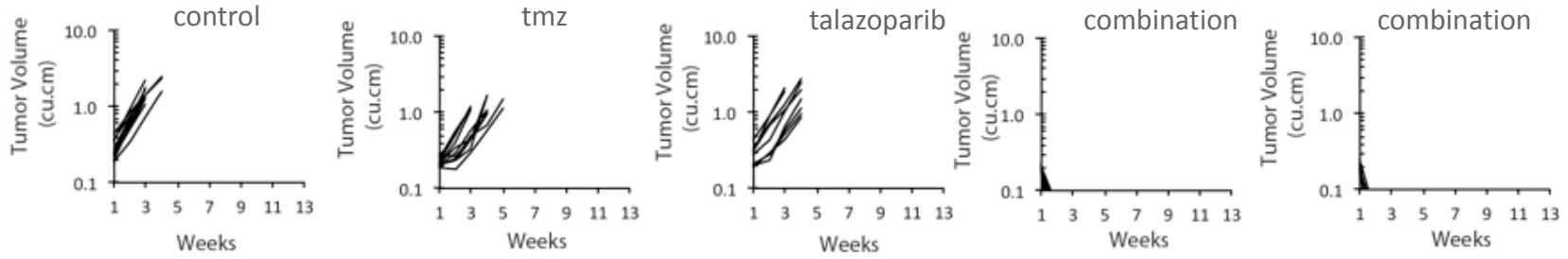
Trapping is important in PARP inhibitor synergy with temozolomide



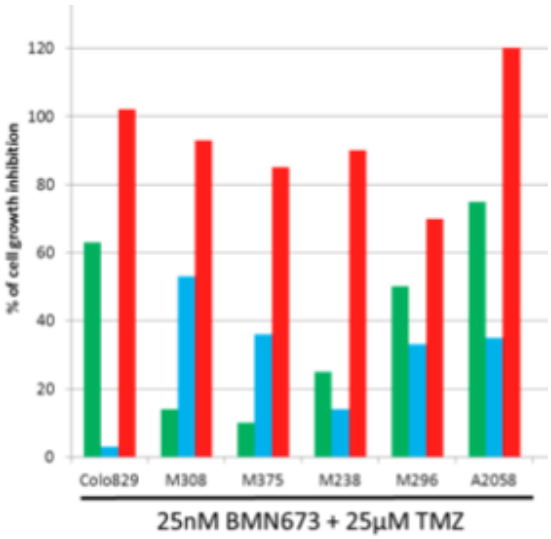
Murai, Pommier, et al JPET 2014

Temozolomide-talazoparib synergy in multiple models Ewing's sarcoma, melanoma, small cell lung cancer

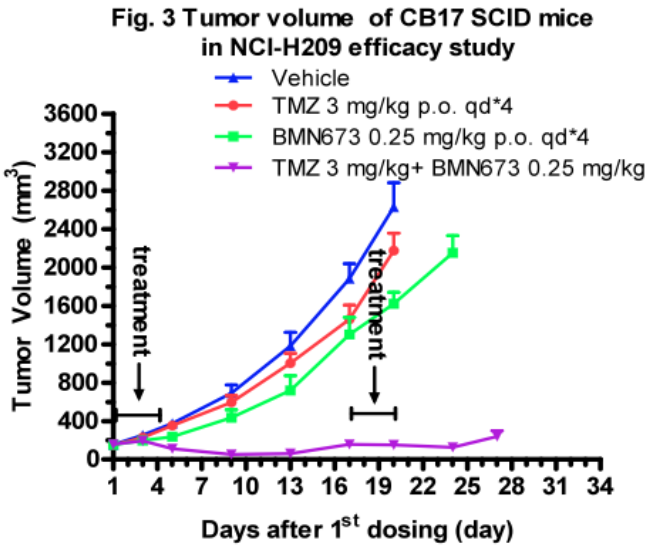
ES-7



Smith et al, AACR 2014



VonEuw, Slamon et al; SMR 2013



Feng et al EORTC 2014

Alternative ways to think about PARP inhibitor combinations with DNA damaging agents

- Traditionally, PARP inhibitors described as “chemosensitizers” or “radiation sensitizers”, i.e., inhibiting repair of DNA damage caused by cytotoxic
- For some types of DNA damage, the cytotoxic may sensitize to the PARP inhibitor trapping, i.e., create sites of DNA damage where PARP is trapped
- True for agents where mechanism of cell killing involves PARP trapping
- Temozolomide excellent candidate
- Many PARP inhibitor clinical combination studies done with full dose cytotoxic, MTD of PARP inhibitor added
- In model where cytotoxic sensitizes to PARP inhibitor, should use full dose PARP inhibitor for maximum PARP trapping, with MTD of cytotoxic added to create damage sties for trapping
- Basis for COG and UCLA trials

Two ongoing clinical trials testing talazoparib plus temozolomide

- **PARP Inhibitor talazoparib and Temozolomide or Irinotecan Hydrochloride in Treating Patients With Locally Advanced or Metastatic Solid Tumors**
- Sponsored by Jonsson Comprehensive Cancer
- PI: Zev A Wainberg, UCLA

- **Talazoparib and Temozolomide in Treating Younger Patients With Refractory or Recurrent Malignancies**
- Sponsored by NCI. Conducted by Children's Oncology Group Phase 1 Consortium
- PI: Eric Schafer, Baylor

Talazoparib in 2015

- EMBRACA and ABRAZO trials in BRCA carrier breast cancer
- Single agent study in other DNA repair deficient tumors than BRCA carriers
- Collaborations with Myriad Genetics, Foundation Medicine, others
- Temzolomide and irinotecan combination in ongoing studies
- Additional combinations
- CTEP collaboration, investigator studies

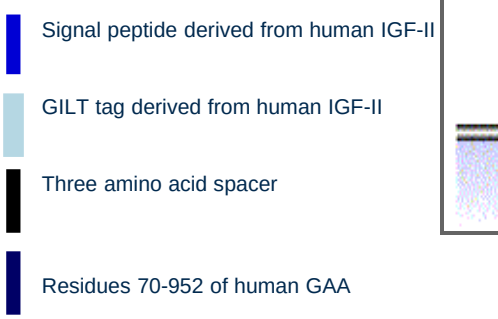
BMN 701 is a IGF2-GAA fusion protein being evaluated as a potential therapy for Pompe disease

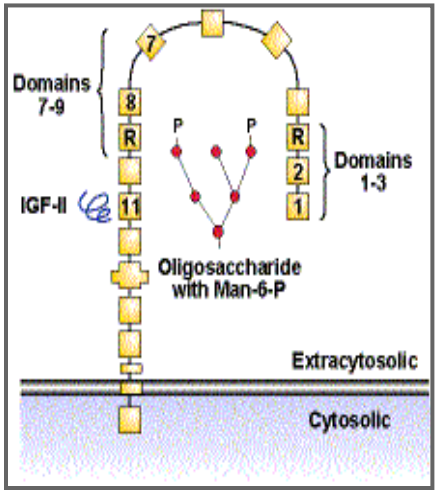
- Pompe is a progressive myopathy resulting in muscle weakness including weakness of diaphragm
- Respiratory impairment occurs early; primary cause of mortality and morbidity
- To slow, stop or reverse myopathy, must get the enzyme where it needs to be, into the cell and into the lysosome
- BMN 701 has GILT tag which leads to greater uptake in cells in vitro compared to rhGAA and more glycogen clearance from muscle of Pompe mice
- 20 mg/kg doses of BMN 701 improves respiratory function in Pompe mice
- Clinically, BMN 701 has been shown to improve respiratory muscle strength by 35.6% over baseline, compared to 8.7% over baseline with rhGAA
- A phase 3 study in patients previously treated with rhGAA has been initiated to evaluate improvements in respiratory muscle strength

BMN 701 uses Glycosylation Independent Lysosomal Targeting (GILT) mediated by the IGF-2 derived tag

- Limitation of current therapy is insufficient Mannose-6 phosphorylation
- Mannose-6-phosphate receptor and IGF-2 receptor are the same protein[3]
- BMN 701 is IGF-2 tagged rhGAA[4]
  - Recombinant chimeric human protein
  - IGF-2 tag on every GAA molecule targets lysozyme



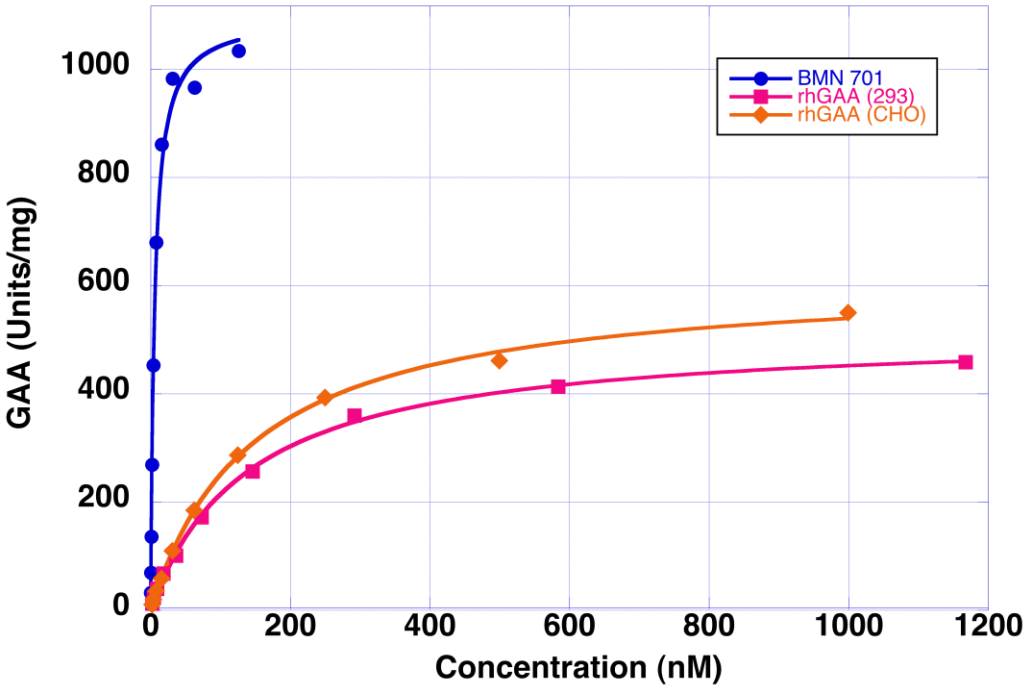


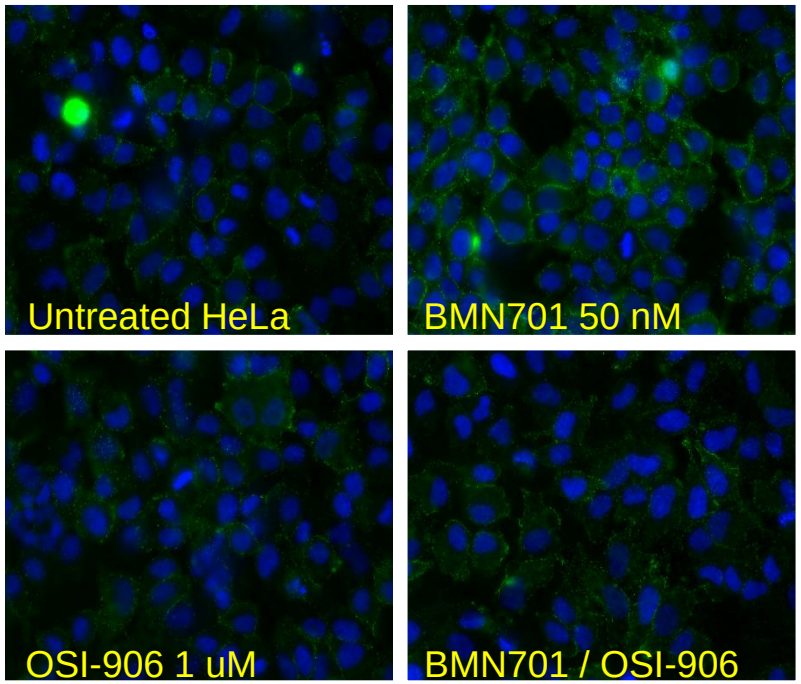


CI-MPR= calcium independent mannose-6-phosphate receptor

3. Tong et al J Biol Chem 1987, 263, 2585-88
4. Maga et al J Biol Chem 2013, 288, 1428-38

Advantages of GILT tagged BMN 701





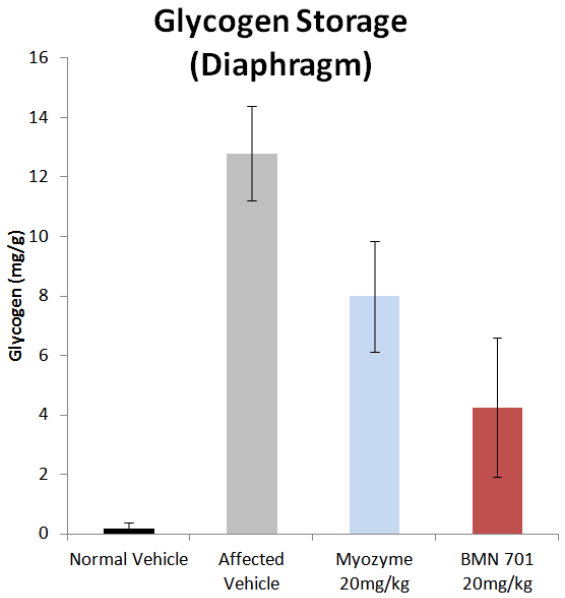
Cell surface CI-MPR increases in HeLa cells after 701 treatment.

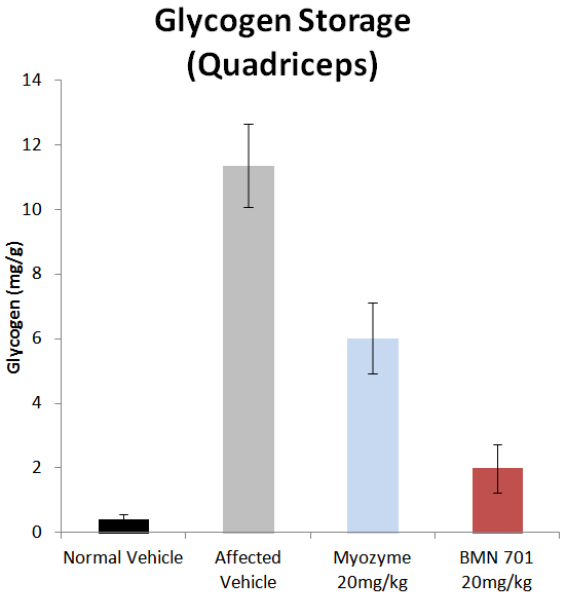
- More delivery of ERT to the lysosome
  - The presence of a high affinity ligand on every molecule means more efficient uptake (lower K_{uptake}) [4]
  - The GILT tag causes an increase in the amount of the CI-MPR on the cell surface via a signaling cascade through the IGF1 receptor (higher V_{max}) [5, 6]
- GILT-mediated vasodilation could improve peripheral ERT delivery
  - May counteract the effect of ACE genotype (under investigation)

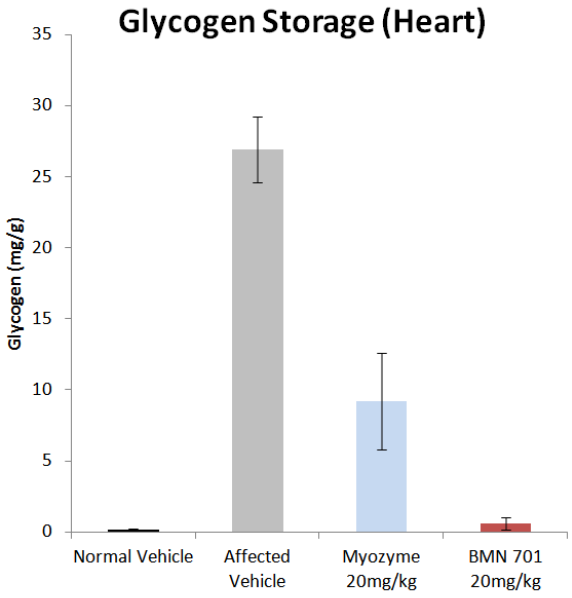
[4] Maga et al J Biol Chem 2013, 288, 1428-38; [5] LeBowitz et al WORLD/LDN, San Diego, 2013; [6] Terrence Satterfield, unpublished

BMN 701 clears muscle glycogen more efficiently than rhGAA in Pompe mice

- Clearance of muscle glycogen with 20 mg/kg BMN 701 is 2-5x better than that achieved with 20 mg/kg of rhGAA in Pompe mouse model ($p < 0.05$)
- Mouse model of Pompe disease (GSD Type II: GAAtm1Rabn/J)
- IV injections: weekly x 4 weeks

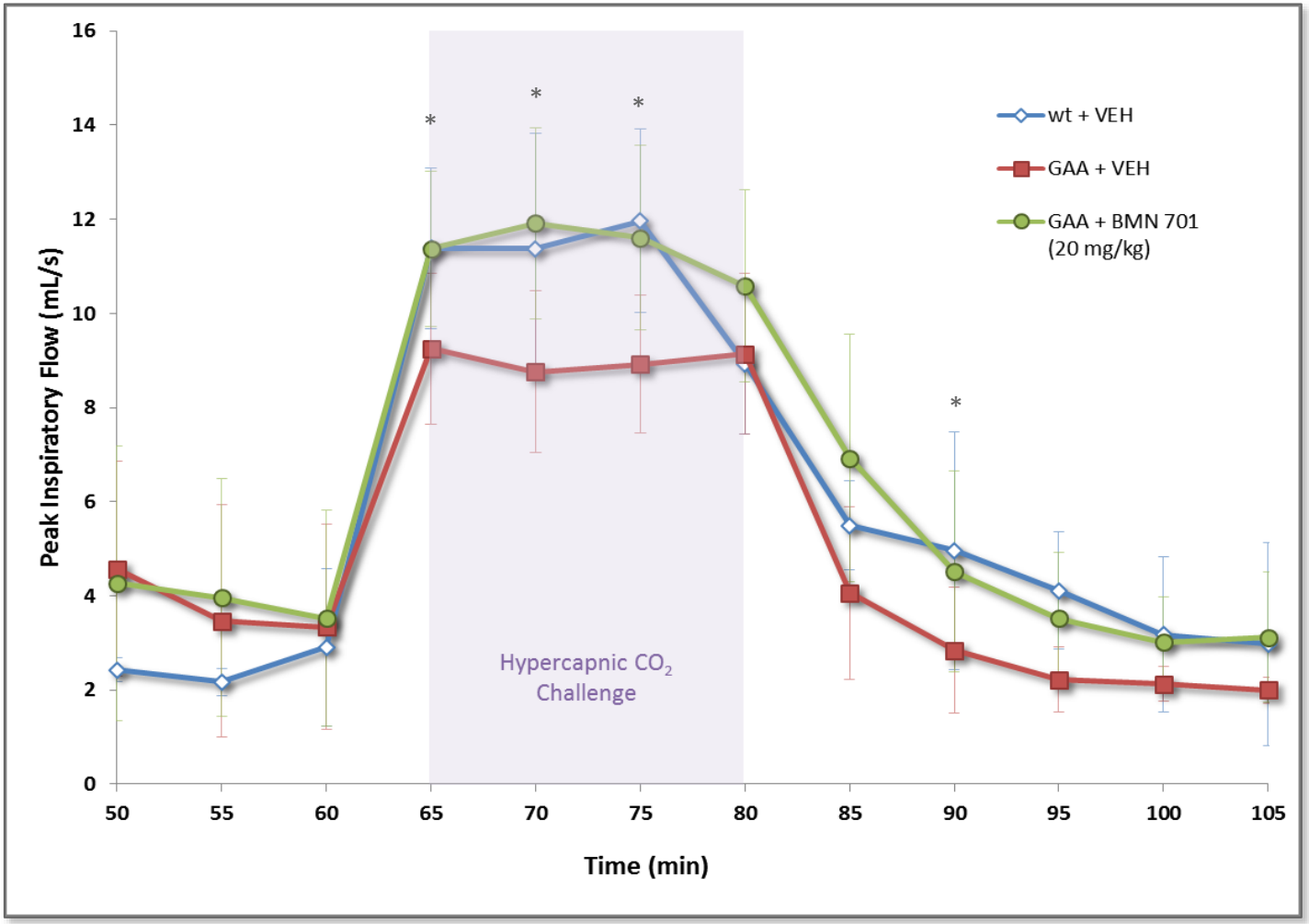






Peng et al. ASHG 2011

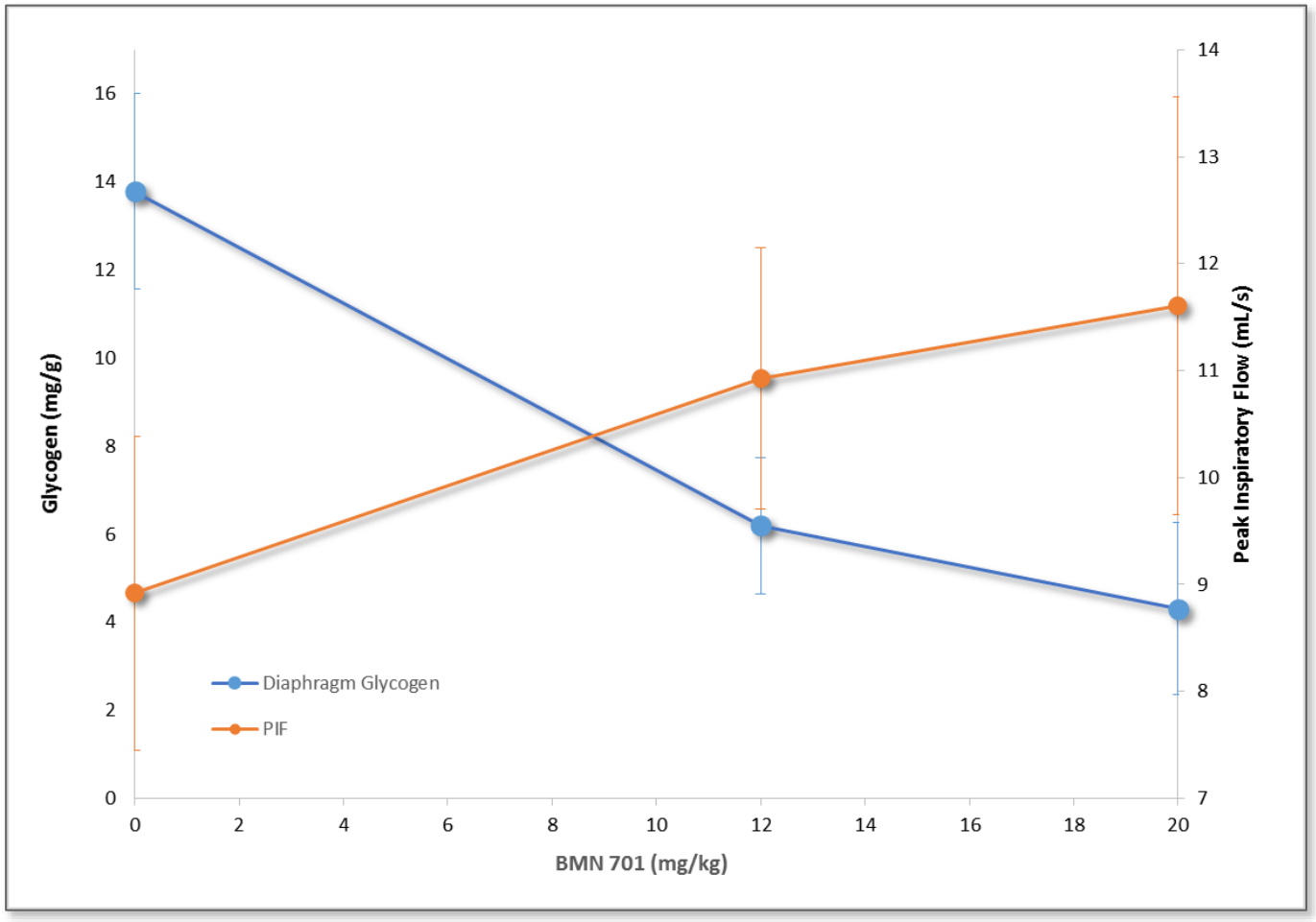
BMN 701 treatment improves Peak Inspiratory Flow in Pompe mice



Tsuruda et al, SSIEM 2014

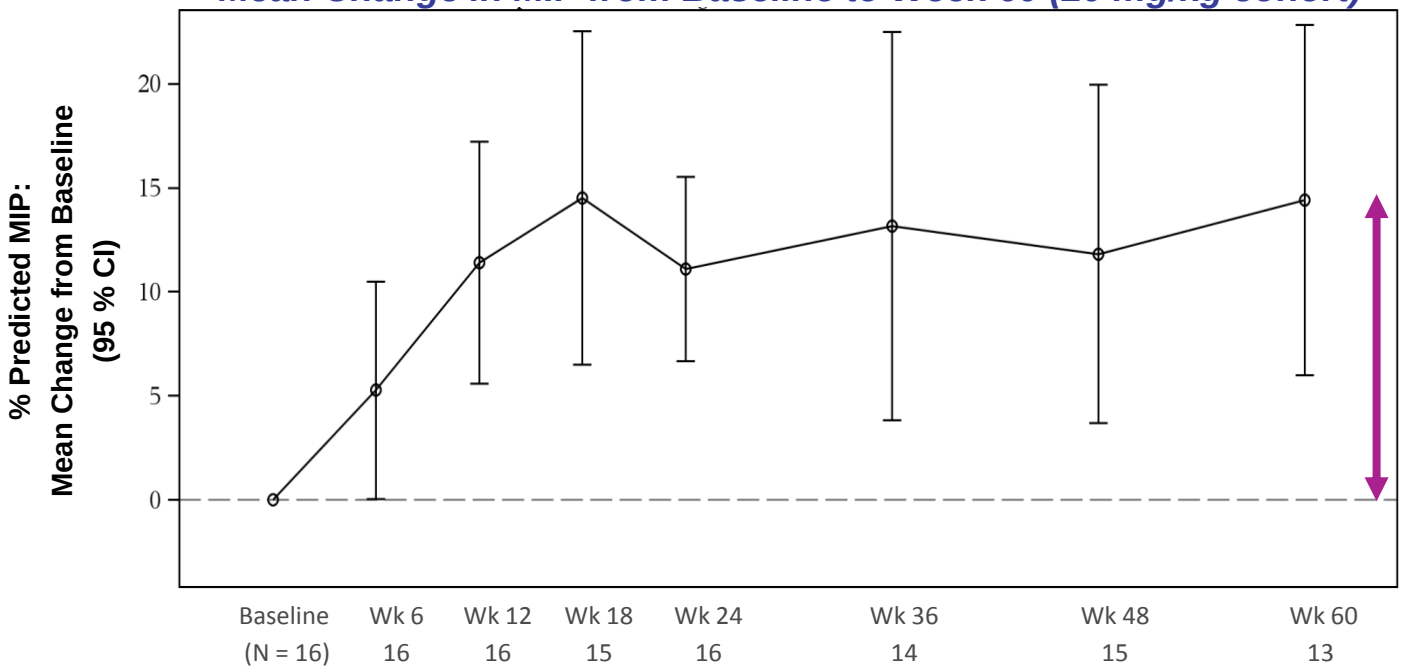
*p<0.05 vs Pompe + VEH

Improvement in PIF is Inversely Correlated to Diaphragmatic Glycogen Clearance



BMN 701 improvement in respiratory muscle strength maintained through Week 60

Mean Change in MIP from Baseline to Week 60 (20 mg/kg cohort)



Mean relative change from baseline to week 60:

35.6%

At week 24, 15 out of 16 patients maintained/improved measure of respiratory muscle strength

At week 60, 12 out of 13 patients demonstrated similar improvement

Byrne et al 2014, WORLD/LDN, San Diego, CA

BMN 701 Clinical Program Overview

301
Phase 3 Switchover Trial
N = 50

901
Global Observational Study
N = 100

201
Transdiaphragmatic Pressure Study
N = 15

Retrospective Analyses
Pre-clinical studies
MIP Meta-Analysis

Goal is to determine the effects of BMN 701 on respiratory muscle strength

BMN 701:
Manufacturing Improvements to Enhance Outcome

- Introduced product into clinic earlier this year with commercial quality
  - Appropriate sialic acid content
  - Analytic profile suitable for human use
  - Comparable if not better pre-clinical efficacy in relevant model
- New process improvement led to:
  - Increased purity
  - Optimized potency and method of analysis
  - Improved cost of goods, capacity and throughput

BMN 701:
Manufacturing Improvements Drive Timeline Change

- Incorporating into Phase 3 3Q15 to support commercialization, with trial paced to have adequate patients on final process material to be commercialized
  - Plan is to enroll 20 patients by 1Q15 for proof of concept
  - Data readout 4Q15
  - Resume enrollment using new manufacturing process thereafter
- Agreement Reached on Analytical Comparability Plans with FDA and EU Authorities



GLOBAL COMMERCIAL OPERATIONS

BIOMARIN ANALYST AND INVESTOR DAY 2014

Jeff Ajer, Chief Commercial Officer
BioMarin

BioMarin: delivering first in class or best in class therapeutics that provide significant value to patients and physicians

- A focus on rare, genetic disorders with a high degree of unmet medical need
- Unique or highly differentiated products

Commercial mission: *Dedicated to helping patients and clinicians achieve better outcomes managing rare diseases including, but not limited to, the appropriate use of BioMarin therapeutics*

Naglazyme® (GALSULFASE)

VIMIZIM® (elosulfase alfa)

KUVAN® (sapropterin dihydrochloride) Tablets

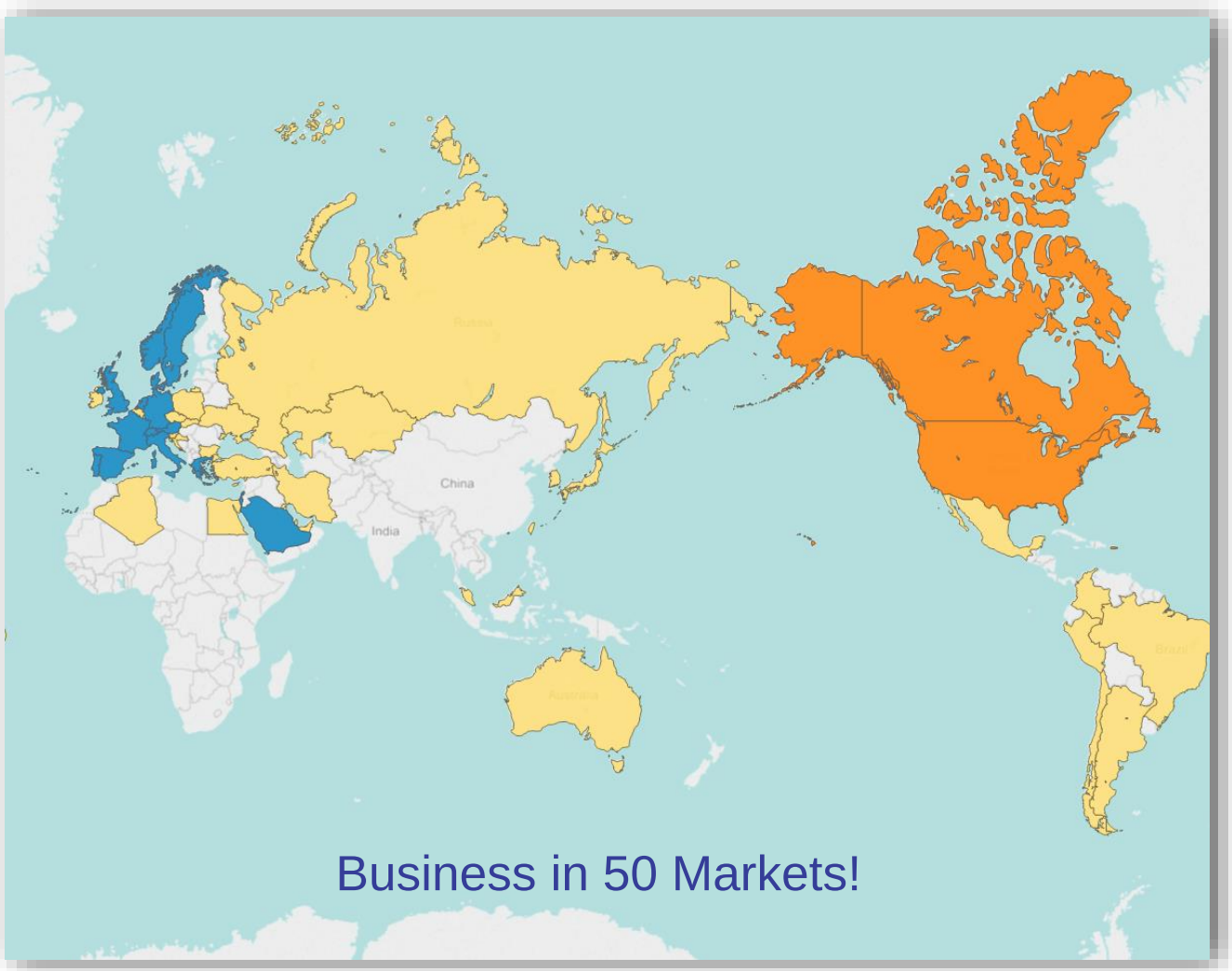
FIRDAPSE™ amifampridine

Strategy for Growth

Executing on our Commercial Investment Thesis

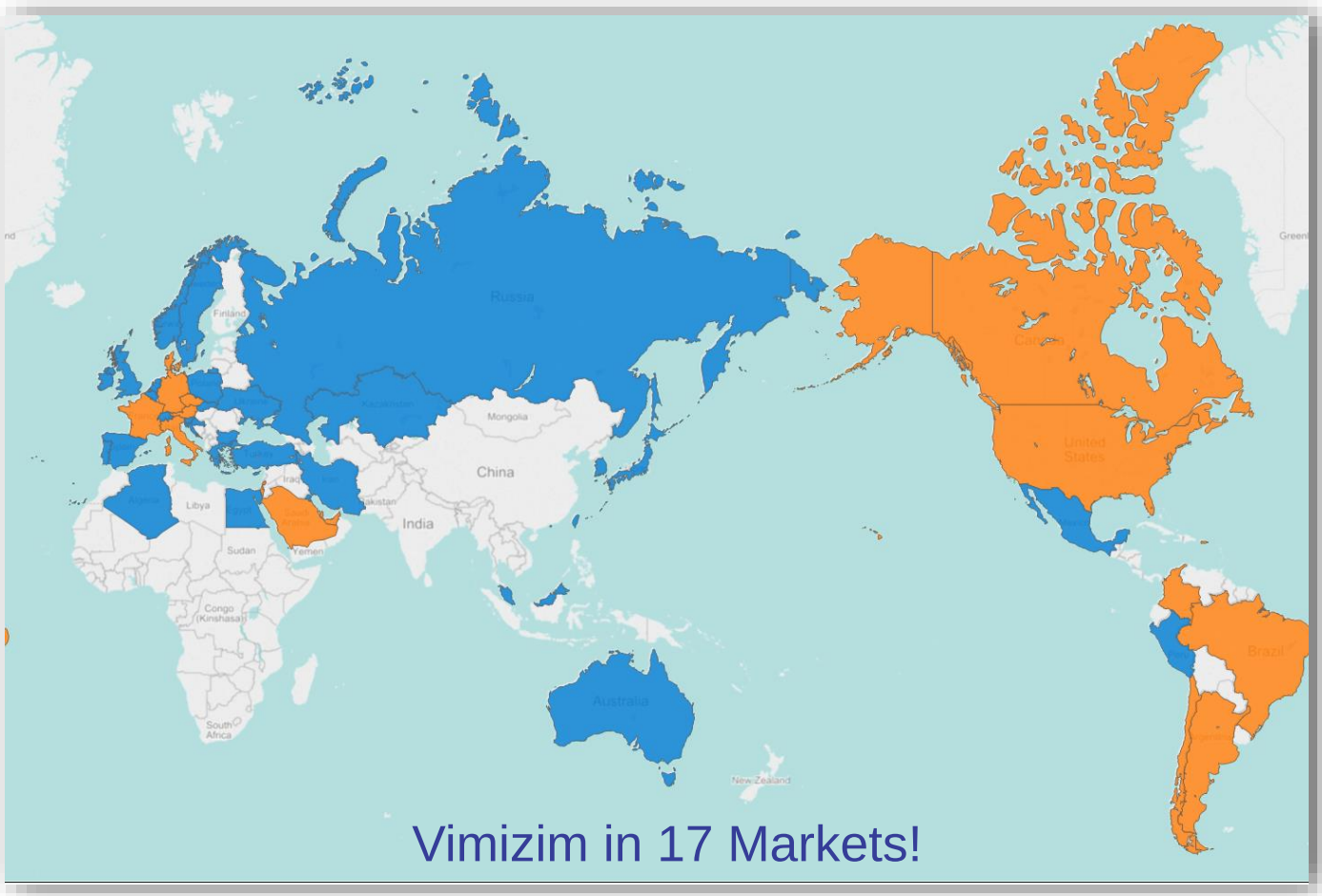
One year ago…	**Today….**
Anticipating Advisory Committee Review for VIMIZIM®	Approval 2Q14; global launch underway
VIMIZIM pricing expected to be $250K-$400K	VIMIZIM priced at ~ $380K/year
1400 MPS IVA patients identified	Over 1650 MPS IVA patients identified
Total BioMarin Revenue FY13 $548.5M	Guidance of $700M-$710M FY14, up 29%
Naglazyme Revenue FY13 $271.2M	Guidance of $305M-$320M, up 15%
Kuvan Revenue FY13 $167.4M	Guidance of $190M-$200M, up 16%

A History of Global Commercial Success



Naglazyme
plus Kuvan
plus Firdapse

Vimizim: building on success and off to a strong commercial start



- First full 4 quarters (2Q14, 3Q14, 4Q14, 1Q15) on the market revenue could exceed $100M
  Objective: Achieve current level of Naglazyme market penetration in half the time
  - Benchmark: 8 years for Naglazyme

Commercial Leverage: Driving Rapid Uptake

Leverage delivers faster and deeper penetration to target markets

- Learning from the Vimizim launch

- PEG PAL: a perfect fit into U.S PKU organization
- Programs falling into rare disease selling model:

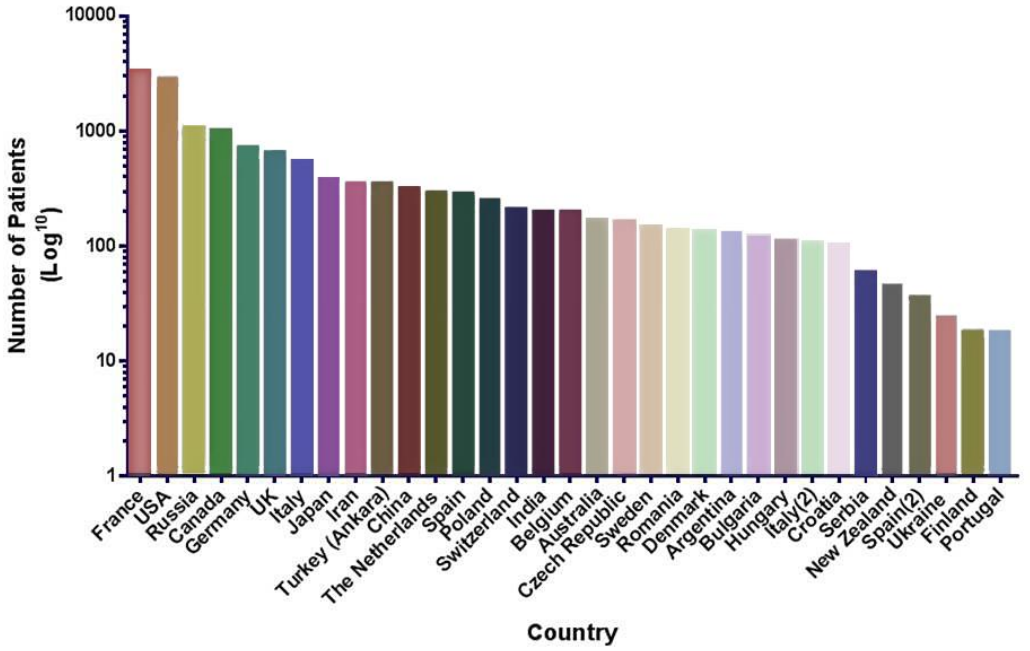
  BMN701, BMN190, BMN111



DMD epidemiology is well-defined, with many patients already identified and followed

- **Most frequently occurring pediatric muscle disorder[1]:** 1 in ~5,000 male births will have DMD[2]
- **Still a rare disease:** we estimate as many as 75,000 boys are living with DMD in our current commercial markets[3]
- **Exon 51 represents 13% of DMD patients[4]:** an estimated 2,000 boys in the US and 2,500 in the EU have mutations that make be eligible for an exon 51 therapy
- **Ongoing global effort to identify and follow DMD patients:** TREAT-NMD has created a registry that follows over 13,500 patients worldwide[5]

Over 13k DMD boys followed in global TREAT-NMD registry[5]

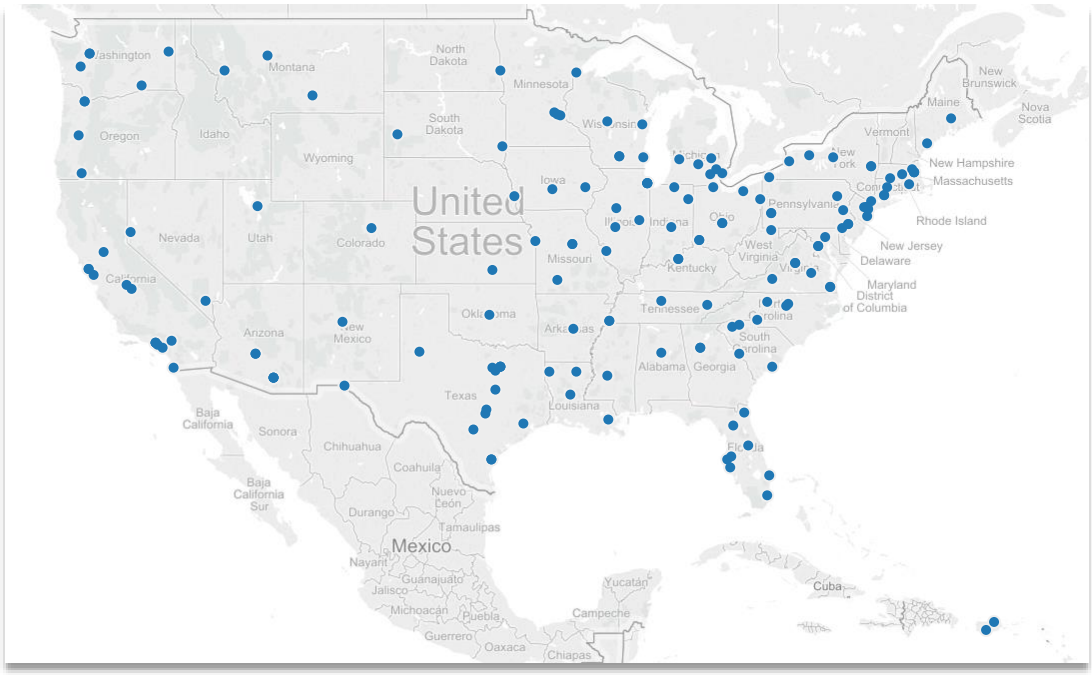


[1]Ahn *Nat Genet* 1993
[2]Mendell *Ann Neurol* 2010
[3]Mah *J Neuro Muscular Disorders* 2014
[4]Aartsma-Rus *Hum Mutation* 2009
[5]TREAT-NMD

DMD fits into BioMarin rare disease commercial model

- **Locus of care is at specialized centers in US and EU:** neuromuscular specialists serve to diagnose disease, monitor progression, and coordinate multiple aspects of care
- **Addressable call point:** 200 MDA clinics in the US, 100 specialized centers in core EU markets, and a limited number of identifiable pediatric neuromuscular specialists represent universe of treaters[1,2]
- **Emphasis on coordination is similar to our other products:** guidelines support multidisciplinary approach to disease management, similar to our PKU and MPS franchises[3]

200 MDA Clinics across the US act as primary point of care in DMD[1]

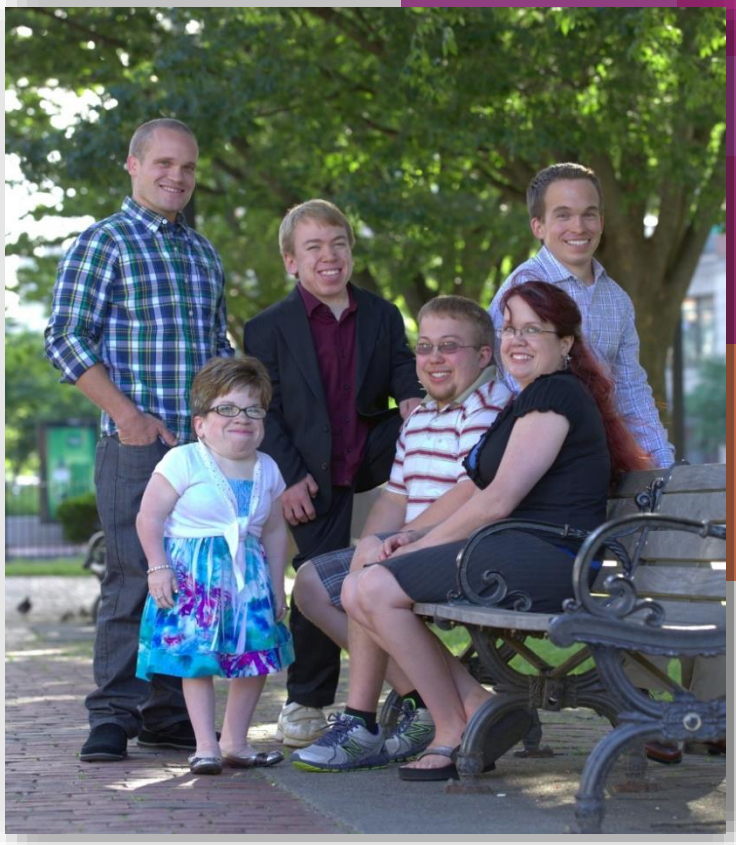


Expect significant commercial leverage

[1]MDA database
[2]Internal market research
[3]Bushby *Lancet Neurol* 2010

BioMarin's commercial model: a focus on patients

- The nature of diseases that our drugs address
  - Very small number of patients
  - High unmet medical need
  - Resulting economics



BioMarin's Model: Find, Start, Keep

Find:

- Very small number of patients
- New patients = market expanders
- Commercial activities:
  - Disease awareness
  - Targeted population screening
  - Patient outreach
  - Patient events



BioMarin's Model: Find, Start, Keep

Start:

- Three key stakeholders all need to be aligned affirmatively:
  - Clinician
  - Patient/family
  - Payer
- Key Considerations
  - Treatment benefit
  - Safety
  - Reimbursement
  - Time and lifestyle commitment



BioMarin's Model: Find, Start, Keep

Keep:

- Successful treatment trial
- Compliance
- Persistence

Patient and service orientation = critical success factor



The History of PKU

PKU first identified



1934

The Guthrie Newborn Test



1960

First use of BH_4 to Tx BH_4 Deficiency



1975

Diet for Life



2000

Kuvan tabs Approved



2007

Kuvan Powder Approved



2014

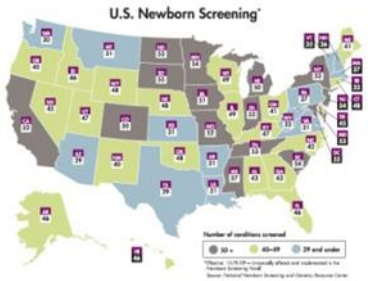
1930 | 1940 | 1950 | 1960 | 1970 | 1980 | 1990 | 2000 | 2010 | 2015

1951



First Medical Food

1967



PKU Newborn Screening

1999



First evidence That BH_4 may help in PKU

2004



Kuvan clinical trials

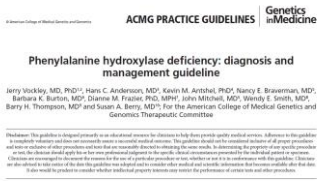
2011

PKU Clinical Coordinators introduced





BMN-165 (PEG-PAL) in P III Clinical Studies



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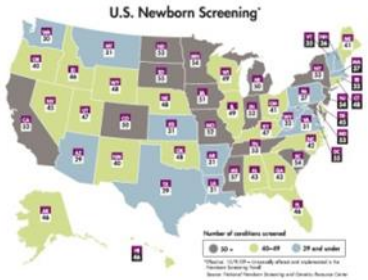
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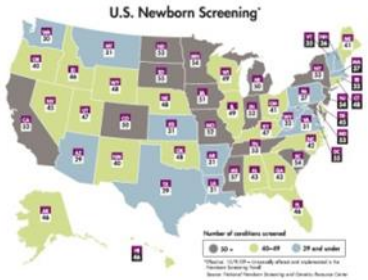
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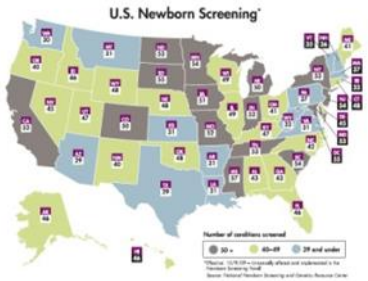
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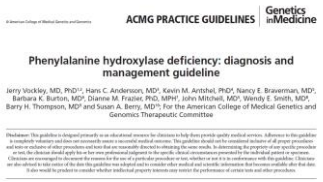
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Kuvan and PEG PAL: complementary therapeutics covering the entire PKU market

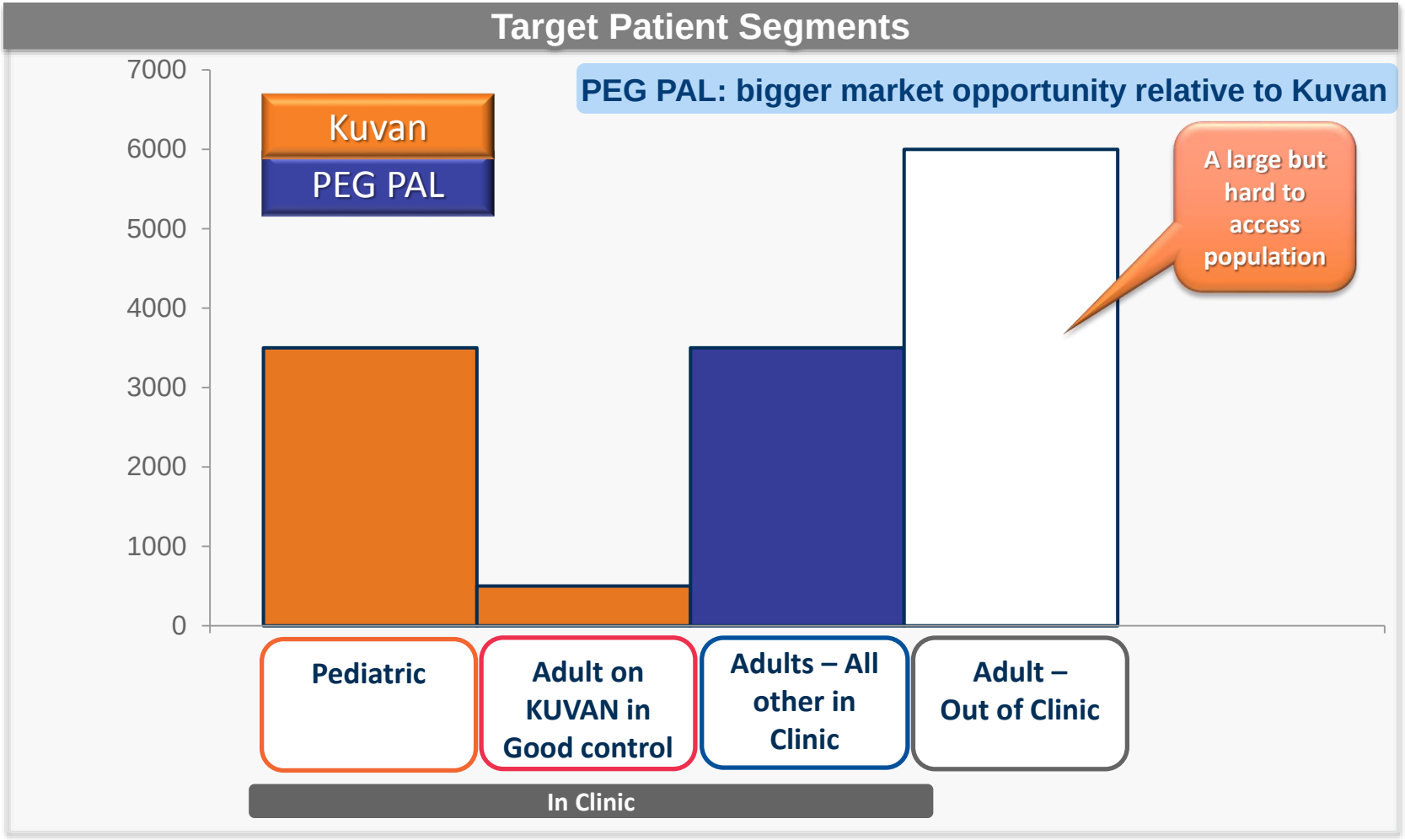




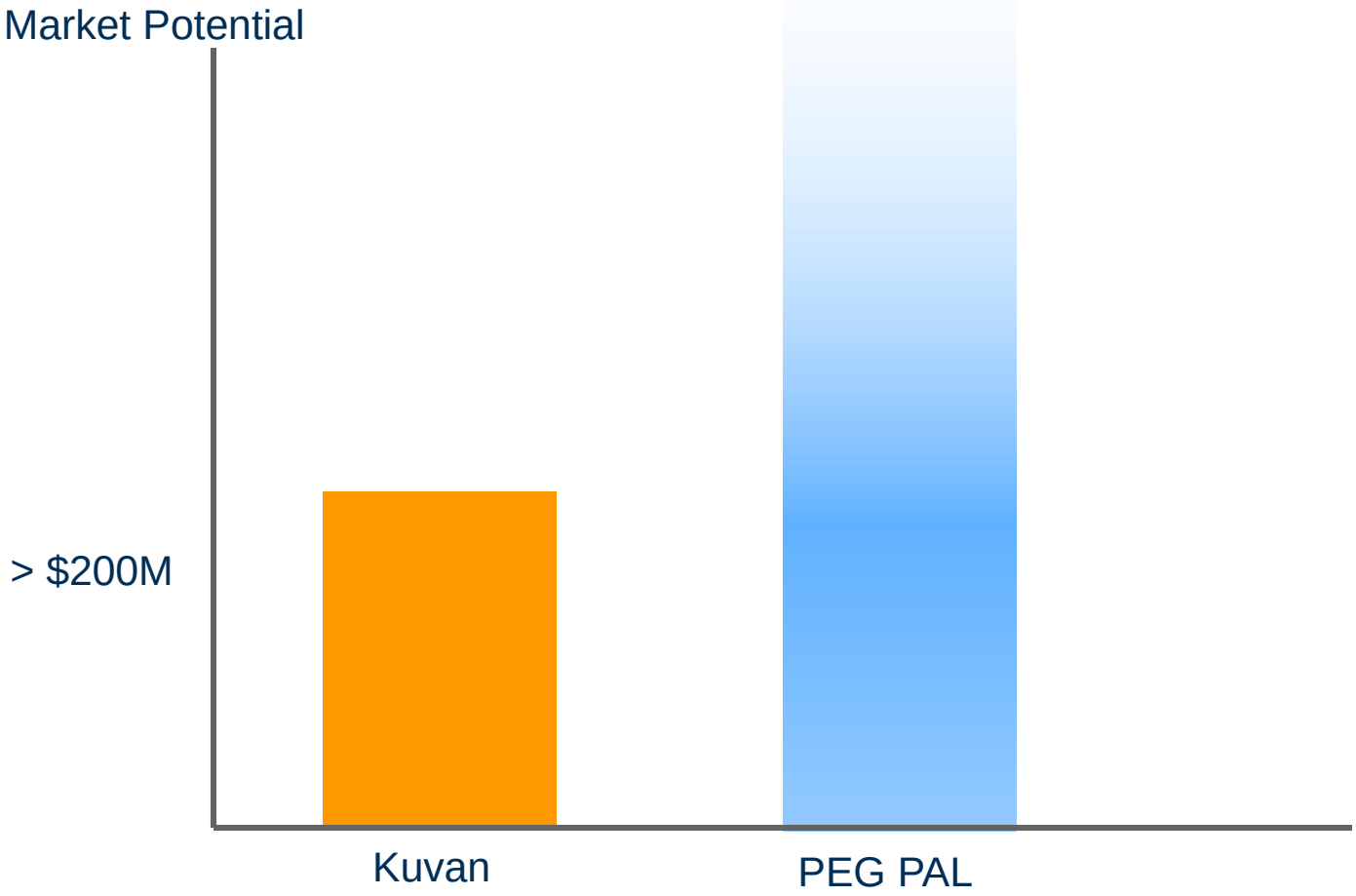


FEATURE	KUVAN	PEG PAL
Route of Administration	Oral Tablets & Powder	Sub Q Injection
Description	Small molecule	Pegylated non-human protein
Mechanism of Action	Enzyme Activator	Enzyme Substitute
Dosage Frequency	Once daily	Once daily
Age range	1 month – 49 years	18 years +
Target Patient	BH4 responsive patients	Adults with elevated Phe

Kuvan and PEG PAL: complementary therapeutics covering the entire PKU market



U.S. PKU Franchise: PEG PAL to Drive Future Revenue Growth



2015 Major Value Drivers

Vimizim – Still in launch mode

- Registrations underway in new markets
- Price and reimbursement approvals in France, Germany, U.K., Japan and secondary markets
- Named patient sales in Turkey
- Increased market penetration in key global markets; U.S., Germany, France, Italy, Brazil, Colombia

Naglazyme – A growing brand 9 years post-launch

- Continued new patient identification coupled with high compliance and persistence = formula for maintaining revenue growth

Kuvan – 2014 was a banner year; expect continued momentum in 2015

- Supportive ACMG guidelines
- Powder formulation
- Field-based clinical coordinators



THANK YOU

BIOMARIN



CLOSING COMMENTS AND Q&A

BIOMARIN ANALYST AND INVESTOR DAY 2014

Jean-Jacques Bienaimé
Chief Executive Officer
Hank Fuchs
Chief Medical Officer

What's New Today?

Drisapersen

- Potential near-term registration opportunity in large market with unmet need
- Seamless fit within BioMarin's clinical, regulatory and commercial expertise

BMN 111 for Achondroplasia

- First 3 cohorts enrolled
- Leveraging the natural history study to inform our understanding of our patients and analytic approaches

BMN 190 for CLN2, Late Infantile Form of Batten Disease

- Enrollment completion imminent
- Current study exhibiting excellent safety profile to date

BMN 270 for Hemophilia A

- Launching Phase 1 study 1H15 on track two years after licensing
- Expanded pre-clinical proof of concept to include "real world" (clotting) assays

What's New Today?

PEG PAL for PKU

- Phe lowering in patients from enriched study at 26 weeks is robust at ~60%
- Enhanced strategies in place to facilitate commercialization
- Pivotal data now expected 1Q16

BMN 701 for Late-onset Pompe Disease

- Improved manufacturing process with better purity, potency and COGS
- Modifying program to leverage "to be commercialized process"
- Proof of concept in 20 patients of switch study; enrollment 1Q15/results 4Q15
- Pivotal study resumes 4Q15

Talazoparib for mBRCA BC

- Enrolling more trials, including talazoparib in combination, neoadjuvant, etc.

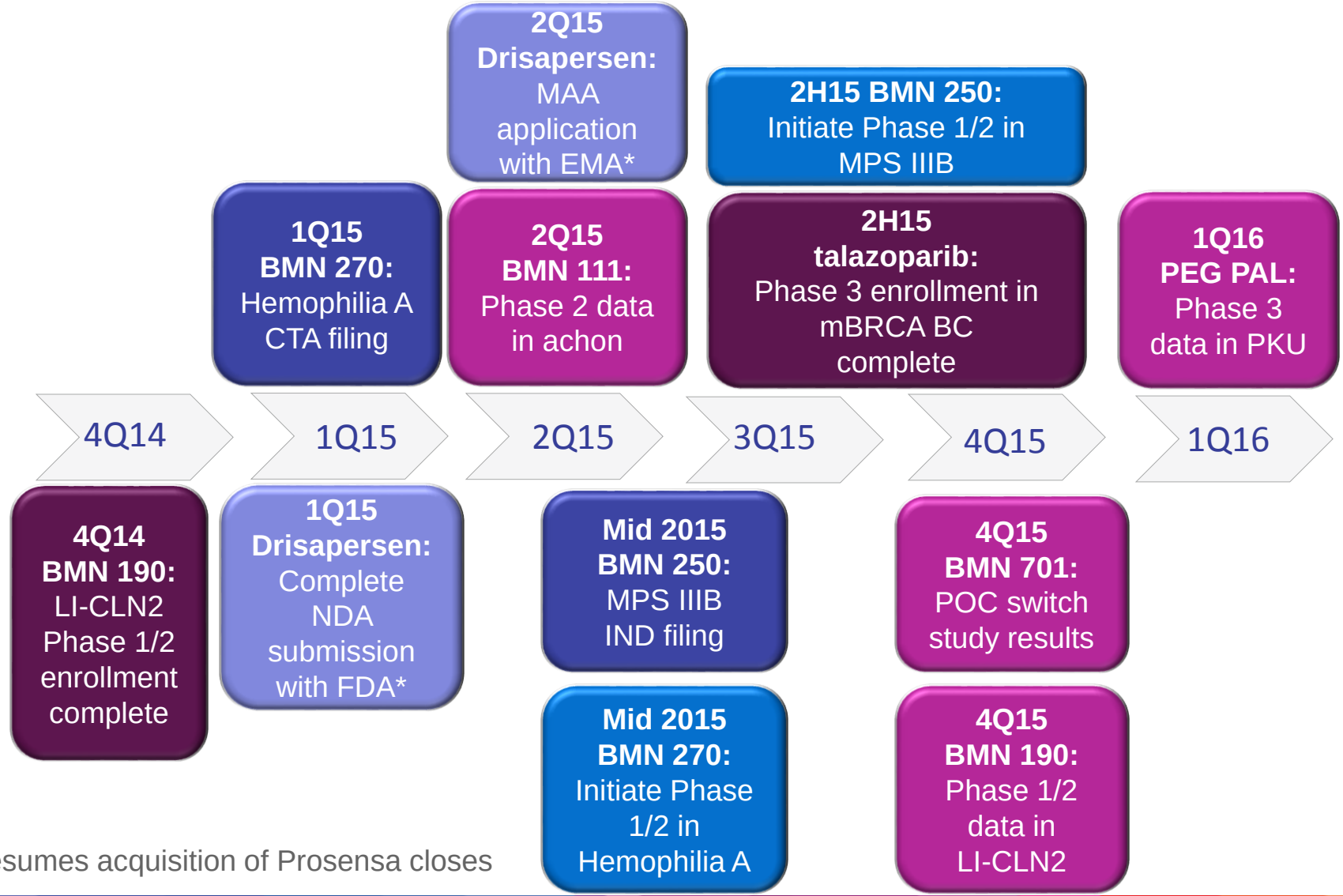
BMN 250 for MPS IIIB (Sanfilippo B syndrome)

- Launching natural history study with patient accrual expected 2015
- Phase 1 study in MPS IIIB patients

Financial Outlook

- Detailed financial guidance to be provided in February 2015 with year-end release
  - Consistent with past practice
  - Will allow for Prosensa budget exercise
- 2015 Revenues: Generally comfortable with consensus estimates
- 2015 Operating Expenses: Consensus R&D and SG&A expenses without Prosensa approximately 5% to 10% too low
- GAAP Operating expenses include substantial non cash expenses
  - 2014 non GAAP loss guidance: $50 million to $65 million
  - 2015 non GAAP loss to be <$100 million
- Prosensa impact. Details to be developed
  - Preliminary estimate $70 million to $100 million of additional operating expenses, primarily R&D
  - Estimate additional $60 million to $70 million of GAAP expense associated with CVR accretion

Advancement across the Development Portfolio



* Presumes acquisition of Prosensa closes



Q&A

Jean-Jacques Bienaimé
Chief Executive Officer

Hank Fuchs
Chief Medical Officer