

Effects of IPLEX in Myotonic Dystrophy Type 1 (DM1)

Muscle Study Group Annual Meeting
9/16/2008,
Beaver Hollow, NY

Richard T. Moxley, III, MD



UNIVERSITY *of*
ROCHESTER
MEDICAL CENTER

Acknowledgements

University of Rochester Medical Center

- Principal investigator: Richard Moxley, III, MD
- Co-investigators: Charles Thornton, MD, Chad Heatwole, MD, Rabi Tawil, MD, Eric Logigian, MD, Stephen Welle, PhD
- Biostatistician : Michael McDermott, PhD
- Clinical Evaluator: Shree Pandya, MS, PT and Katy Eichinger, PT
- Study coordinators: Jim Hilbert, MS, Christine Quinn, MS and Alexis Smirnow
- Data management: Bill Martens.
- Research administration: Nancy Merriman and Tracy Forester
- Research assistants: Roxanne Cannarozzo and Karen Berk.
- Neuro-Ophthalmology: Deborah Friedman, MD

University of Texas Health Science Center, San Antonio.

- Independent Medical Monitor: Carlayne Jackson, MD

Acknowledgements

- NIH Wellstone Muscular Dystrophy Cooperative Research Center (MDCRC) staff, leaders, and members of the DSMB.



National Institutes of Health

The Nation's Medical Research Agency

MDA[®]

Muscular Dystrophy Association



Muscle Wasting in DM1

■ Proposed causes:

- Insulin resistance, gonadal insufficiency, decreased growth hormone release.

■ Unsuccessful trials of

- insulin, testosterone, and recombinant human growth factor (rhGH).

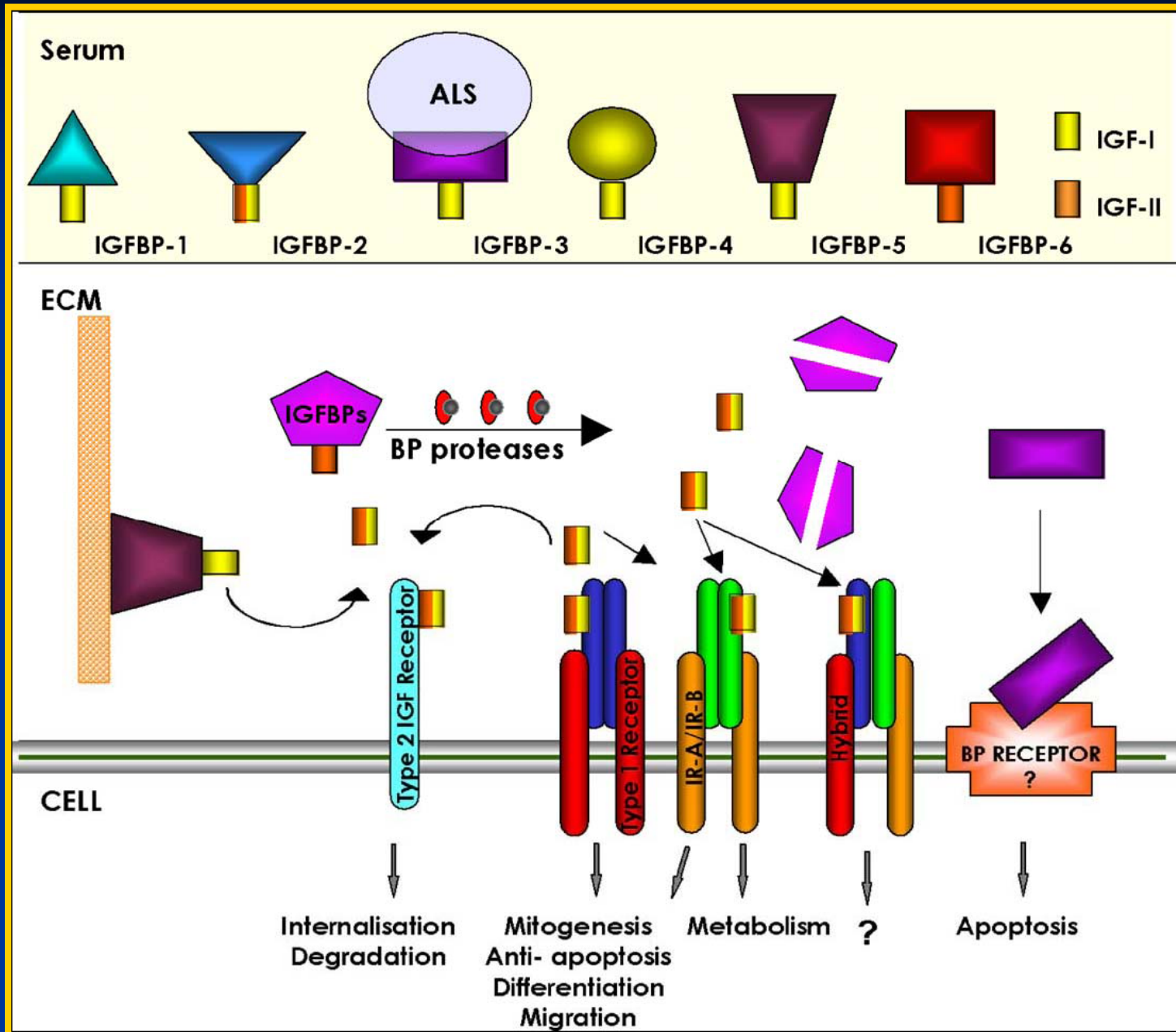
■ Promising results of rhIGF-1 (recombinant human insulin like growth factor) (Vlachopapadopoulou, 1995),

- Improved insulin action, decreased body fat, increased plasma testosterone (n=7),
- But, clinically significant side effects and short half-life.

Insulin Like Growth Factor 1 (IGF-1)

- Family of 6 binding proteins (BPs):
 - At least 5 of 6 BP's form binary complex with IGF-1.
 - Ternary complex comprised of IGF-1, IGFBP-3, and an acid-labile subunit (ALS).
- 95% of circulating IGF-1 is bound to ternary complex.
- Small fraction of IGF-1 is unbound or “free” in circulation.

IGF Schematic: figure from Denley et al. (2005).



Background: IPLEX®

- **IPLEX (Insmed, Inc) is rhIGF-1 complexed to rhIGF-BP3**
 - Longer half-life and better safety profile compared to rhIGF-1.
- **IPLEX has been well-tolerated and effective in:**
 - Severe primary IGF-1 deficiency,
 - HIV associated adipose redistribution syndrome (HARS),
 - Severe insulin resistance,
 - Insulin dependent type-II diabetics,
 - Elderly women with hip fractures.

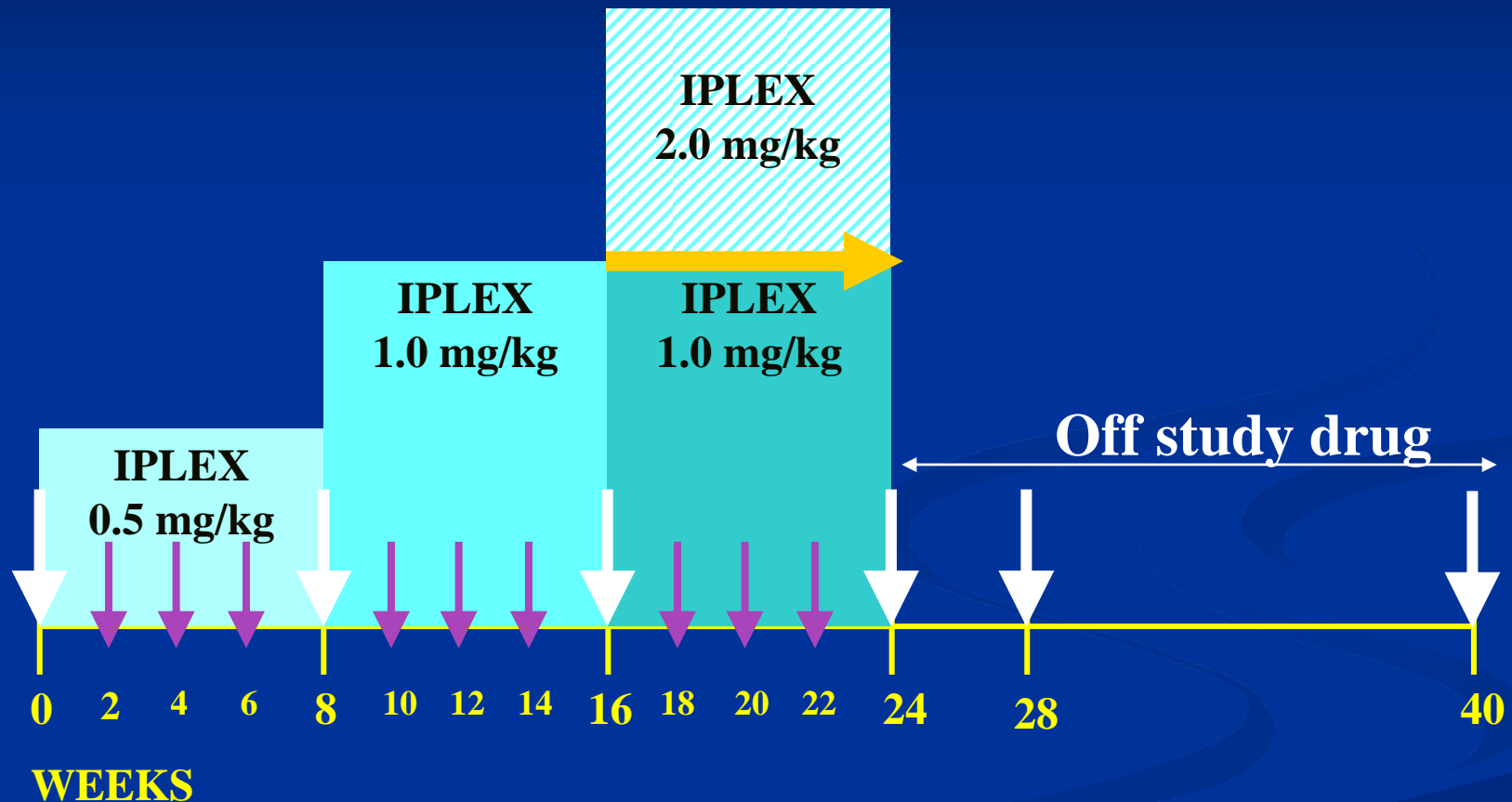
Innovative Approach

- Preparation of IGF-1 that may bypass insulin resistance and other anabolic defects that hamper muscle loss in DM1.

Study Design

- Primary Aim: To determine safety and feasibility of daily SC injection of IPLEX as treatment for muscle wasting and weakness in DM1.
- Subjects: 15 DM1 patients (21-60 yrs of age) each for initial “Dose Escalation” trial.

Design for 24 week Dose Escalation Trial of IPLEX



Cohort of Patients

- **Cohort 1: Completed pilot study (n=6).**
 - 8 weeks of 0.5 mg/kg/day and 16 weeks of 1.0 mg/kg/day of IPLEX.
 - DSMB requested that we obtain data on the relationship between blood levels of IGF-I (at 0.5 mg/kg/day and 1.0 mg/kg/day) and any adverse events before moving to a 3-step dose escalation.
- **Cohort 2: Completed dose escalation of 0.5, 1.0, 2.0 mg/kg/day (8 weeks each) of IPLEX (n=9).**

Outcome Measures

Primary: Safety and tolerability.

Secondary:

- clinical laboratory data,
- lean body mass and fat mass (DEXA),
- muscle strength (QMA and MMT),
- myotonia (grip and electrically evoked),
- IGF-1, IGF-2, and IGF-BP3 levels,
- gastrointestinal and cognitive measurements.

Timeline

■ 2003-2005

- Completed start-up procedures, manual, etc.

■ 2005-2007

- Enrolled patients.

■ September 2007

- Presented at the 6th International Myotonic Dystrophy Consortium (IDMC) Meeting;
- Presented preliminary data on the first 6 patients.

■ April 2008

- Completed all treatment and post-treatment visits.

Results

- Adverse Events and safety profile.
- Total and free IGF values.
- Muscle mass as measured by DEXA.

Adverse Events (AE)

- 1 serious AE (SAE) occurred in the off-drug phase:
 - deemed unrelated (gallbladder removed).
- No SAEs related to study drug.
- 1 moderate, possibly related AE:
 - papilledema and intracranial hypertension that resolved without sequelae.

Adverse Events

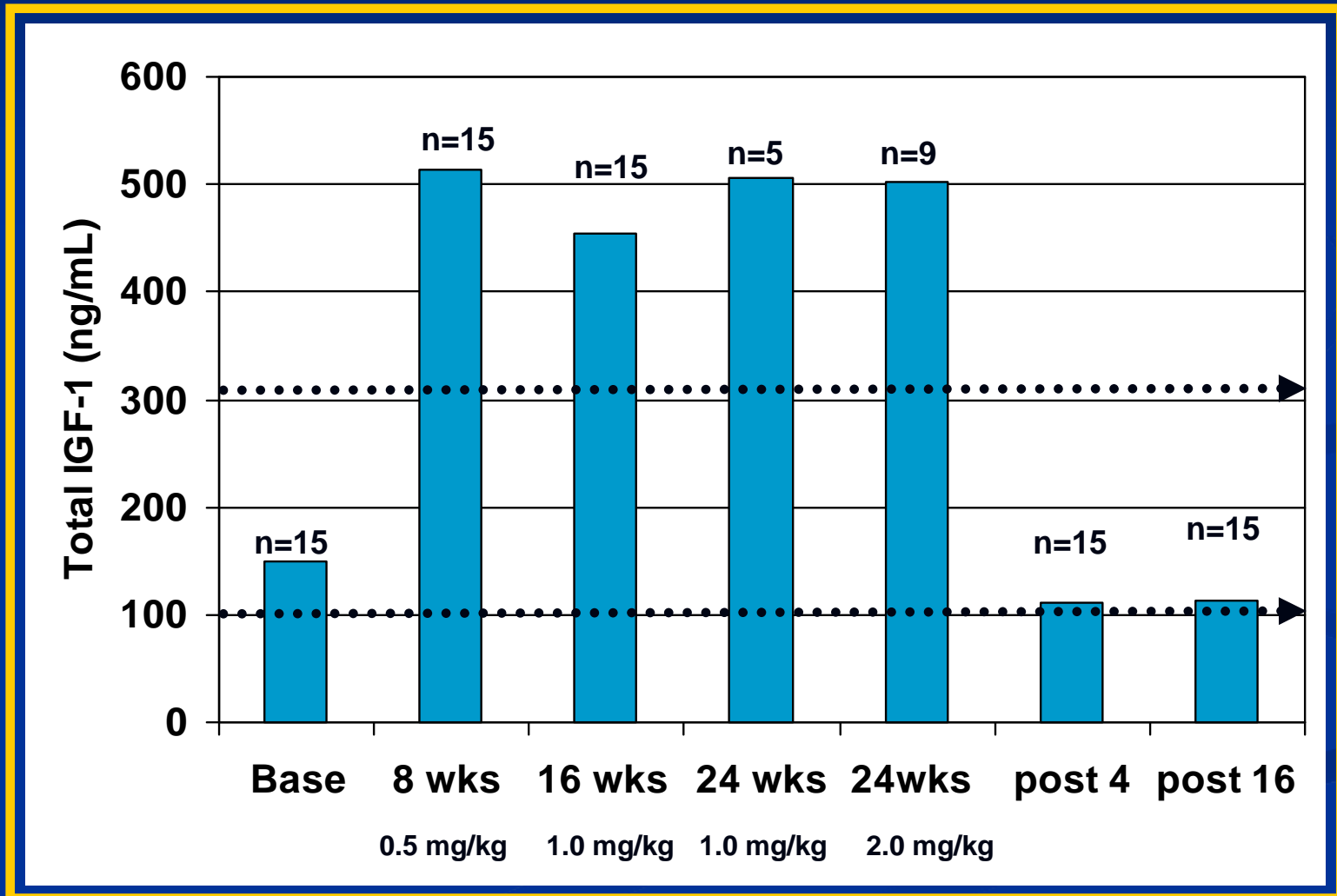
- 103 mild AEs:
 - 42% (n=44/105) were not related,
 - 45% (n=47/105) were possibly related,
 - 13% (n=14/105) were probably related.
- 14 AEs probably related to study drug:
 - 2 AEs of light headedness,
 - 3 AEs of hypoglycemia,
 - 9 injection site reactions (n=8 patients).

Safety Profile

- Of the 9 injection site reactions,
 - 7 occurred at first dose (0.5 mg/kg/day);
 - 2 occurred at second dose (1.0 mg/kg/day);
 - 0 occurred at third dose (either 1.0 or 2.0 mg/kg/day).
- Laboratory and imaging results indicated IPLEX was safe and well tolerated.

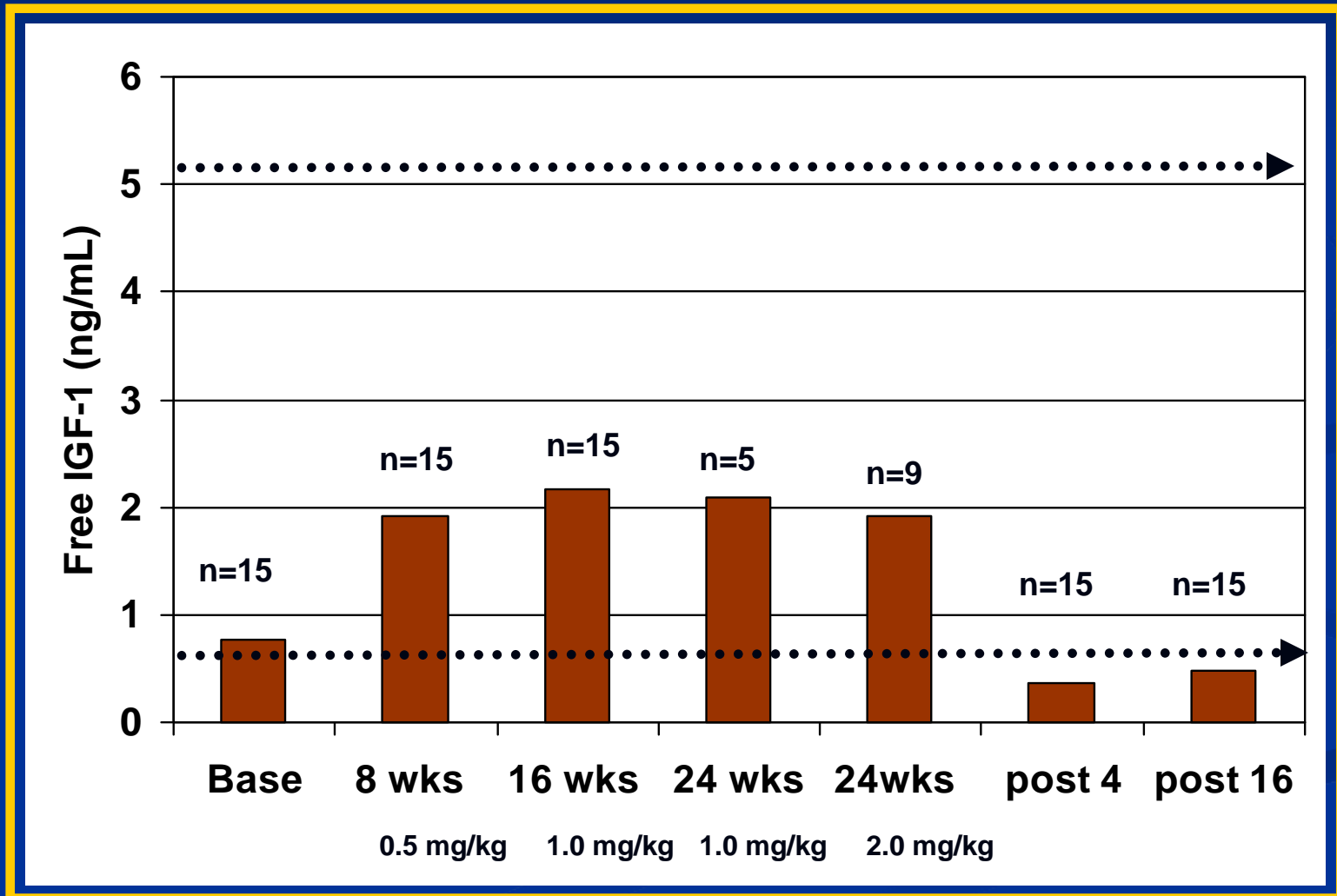
Total IGF-1 values

Fig 1: Mean total IGF-I levels analyzed. Mean normative range indicated as dashed line; 100 – 308ng/mL (Esoterix).



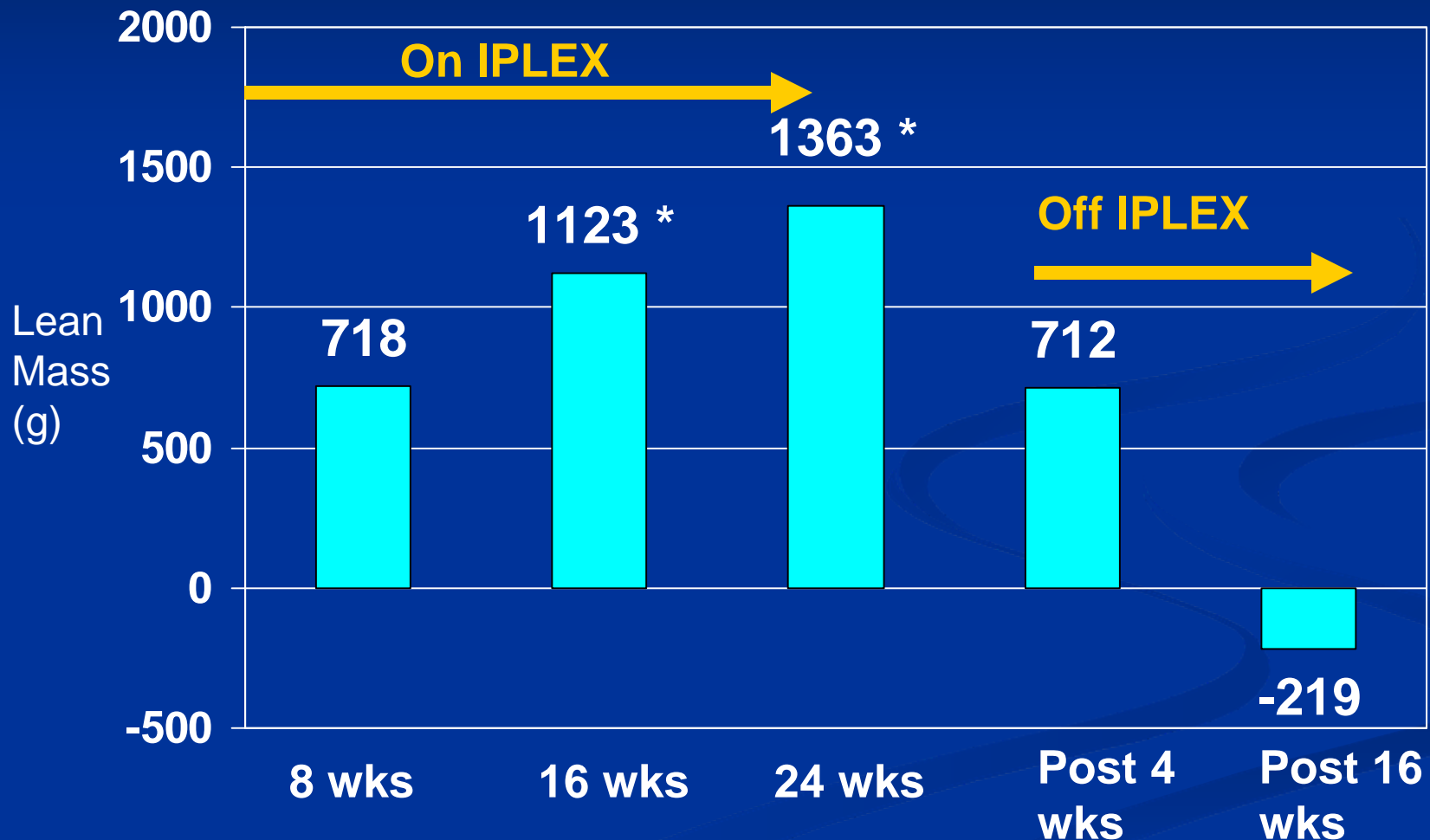
Free IGF-1 values

Fig 2: Mean free IGF-I levels analyzed to date. Mean normative range indicated as dashed line; 0.65 – 5.2ng/mL (Juul et al., 1997).



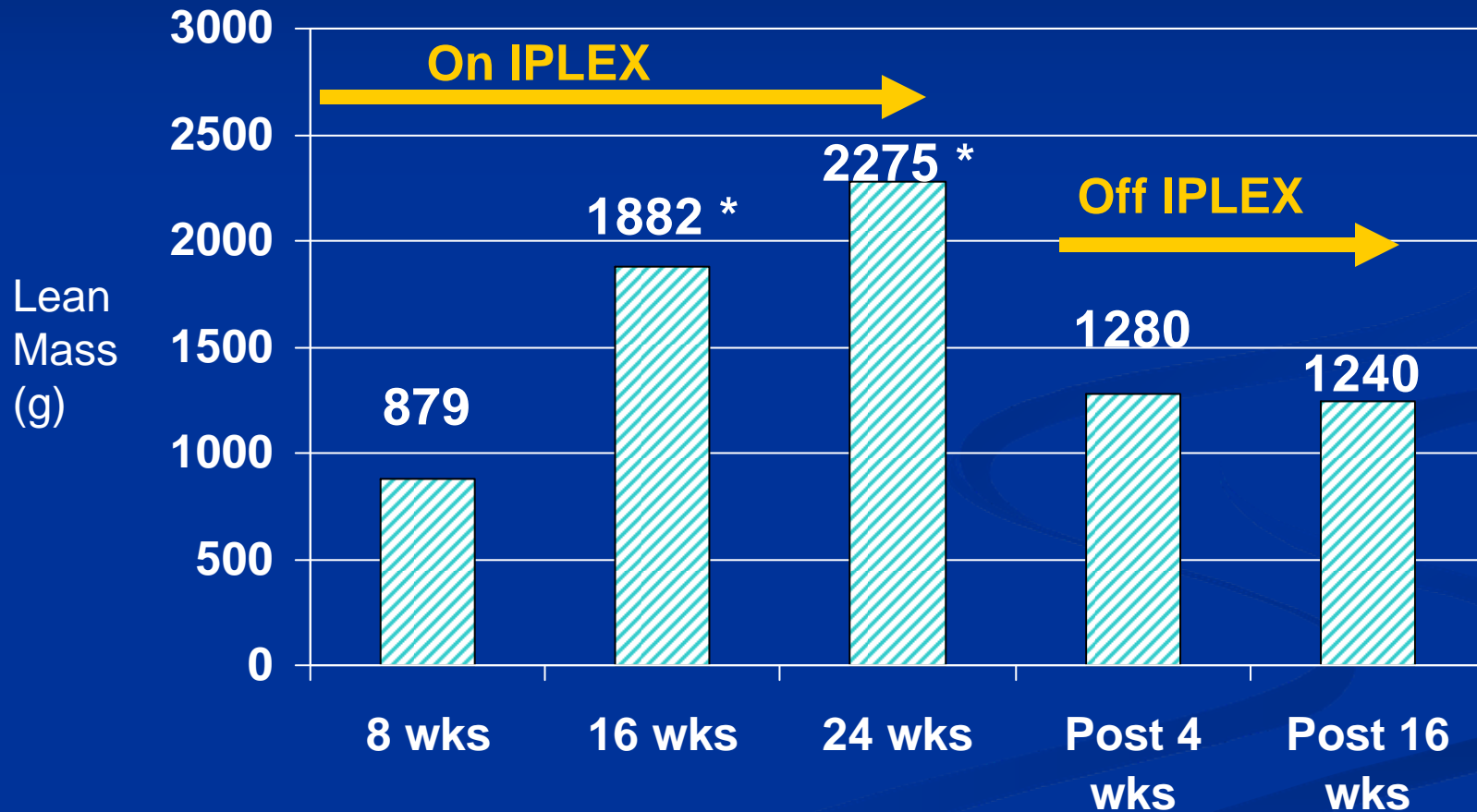
Lean Muscle Mass: Cohort 1

Fig 3: Change in mean lean muscle mass (g) compared to baseline and measured by Dual Energy X-ray Absorptiometry (DEXA) (n=6). * p<0.05



Lean Muscle Mass: Cohort 2

Fig 4: Change in mean lean muscle mass (g) compared to baseline and measured by Dual Energy X-ray Absorptiometry (DEXA) (n=9). * p<0.05



Summary

- IPLEX was safe and well-tolerated in DM1 (n=15 patients).
- Encouraging trends in a variety of endpoint measures, including patient reported outcomes.

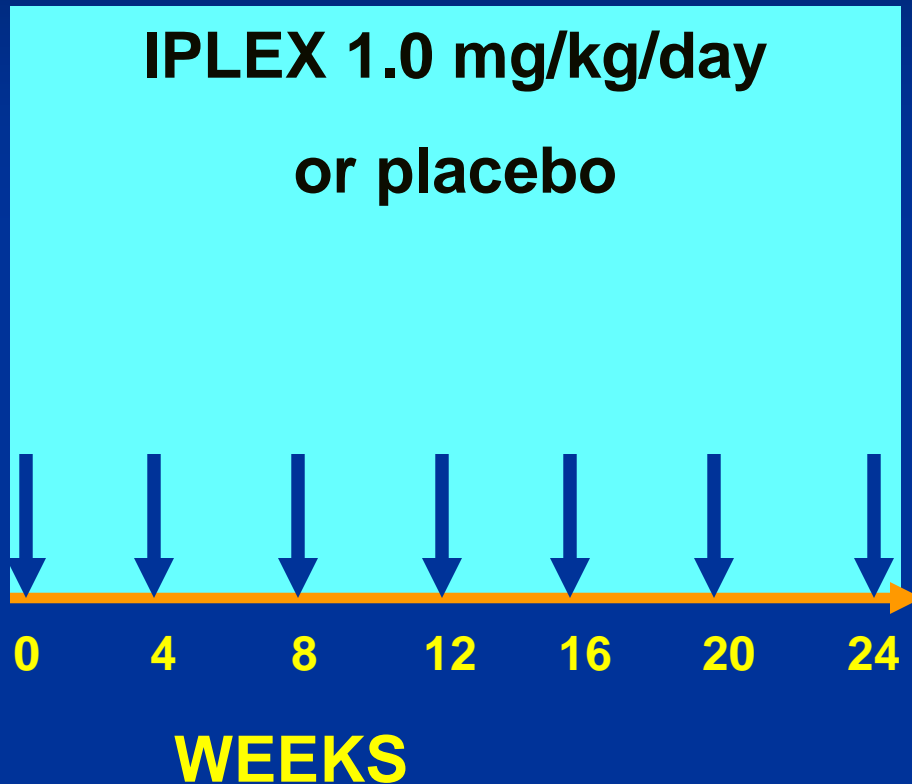
A Catalyst For Future Study

- These initial pilot studies have led to a multi-center collaborative study using methods established by our NIH Wellstone MDCRC dose escalation trial.

Phase II Trial

- Led by Insmed, Inc, with funding through Insmed and Muscular Dystrophy Association (MDA) Translational Research Corporate Grant.
- 12 sites participating in the randomized, placebo-controlled, double-blind clinical study of IPLEX in ~70 DM1 patients.

Study Design



Endpoints:

- Endurance
- Ambulation
- Cognitive function
- Insulin resistance
- Cholesterol and triglycerides
- Muscle function and strength
- Pain
- Gastrointestinal function
- Quality of life

Progress and Collaborations

- Current Phase II trial is beyond the scope of traditional Wellstone funding.
 - NIH Wellstone MDCRC funding has nurtured collaboration between industry, patient advocacy groups, and medical centers.
- What other studies can develop?

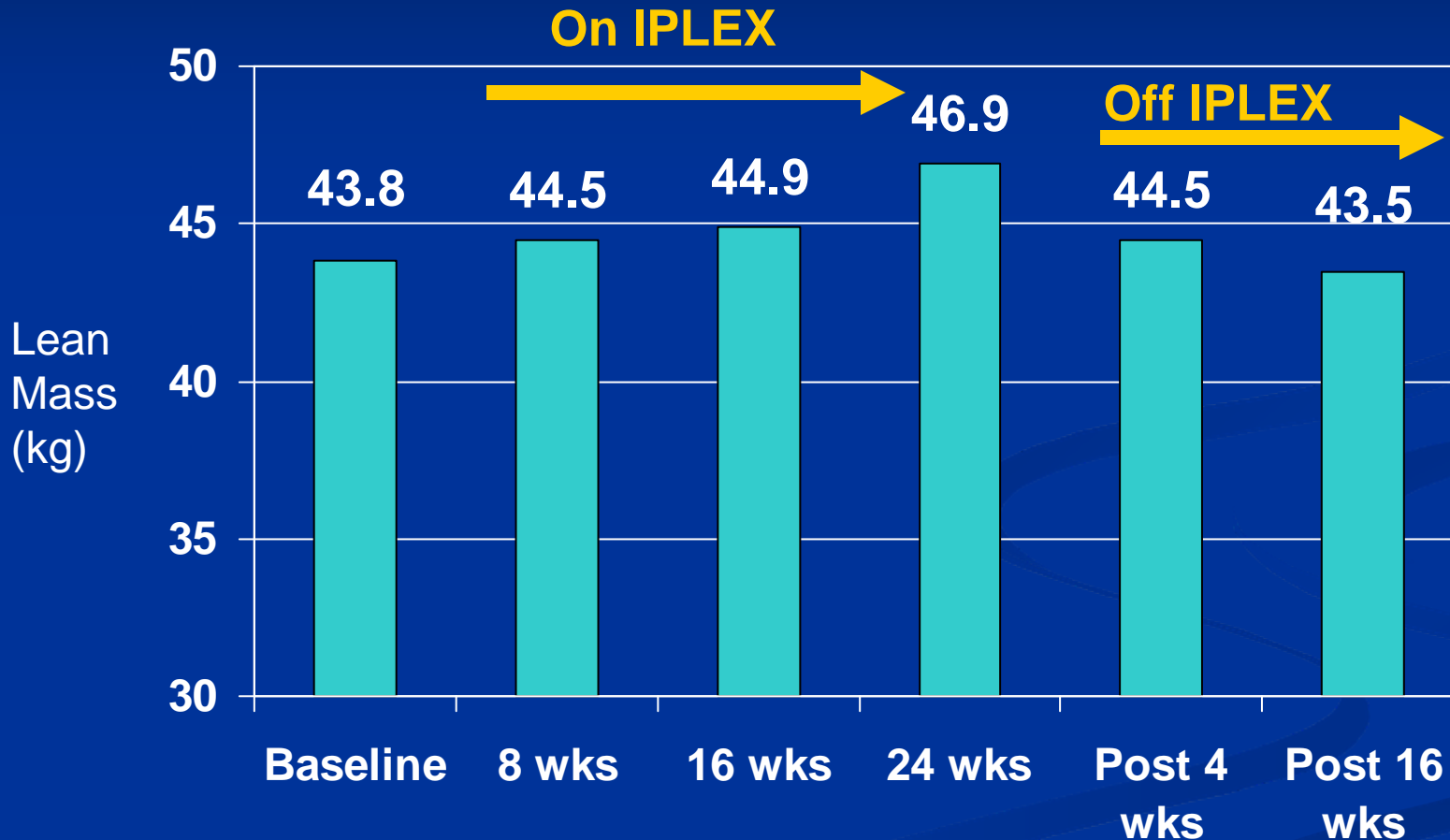
Future Questions

- What measures of IGF-1 and/or related proteins best indicate a therapeutic response?
 - Additional measures may include other IGF BPs, sex steroid BP, growth hormone, and other pituitary-hypothalamic axis hormones.
- What are the best endpoint measures in our optimal dose treatment trial?

Extra slides, drafts

Lean Muscle Mass (Cohort 1)

Fig 2: Mean lean muscle mass (kg) as measured by Dual Energy X-ray Absorptiometry (DEXA) (n=5 for week 24; n=6 all other weeks).



Lean Muscle Mass (change each visit)

Fig 2: Mean lean muscle mass (kg) as measured by Dual Energy X-ray Absorptiometry (DEXA) (n=5 for week 24; n=6 all other weeks).

