Effects of IPLEX in Myotonic Dystrophy Type 1 (DM1)

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Acknowledgements

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National Institutes of Health
The Nation's Medical Research Agency

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Muscular Dystrophy Association

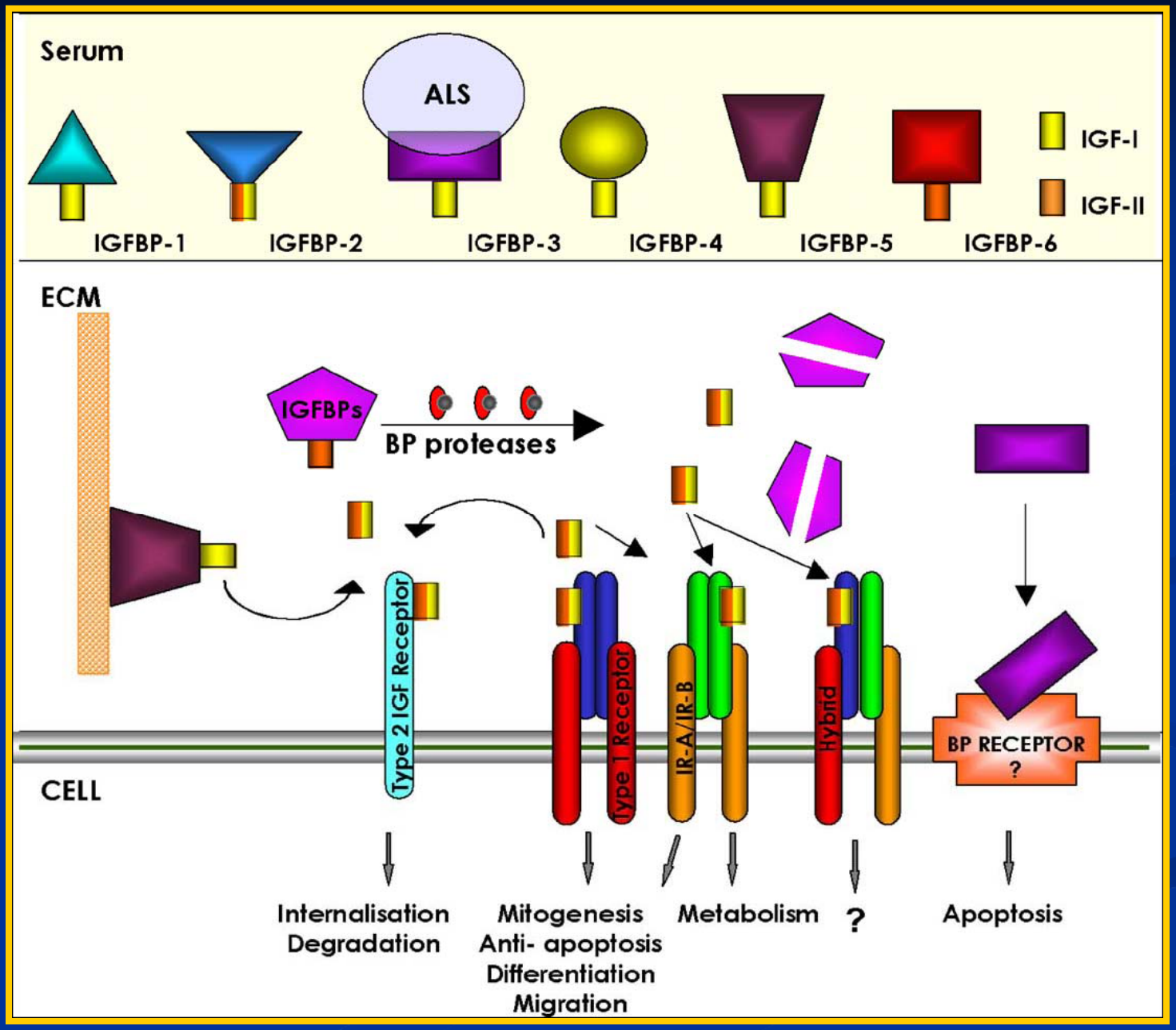
Muscle Wasting in DM1

- **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 at el. (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

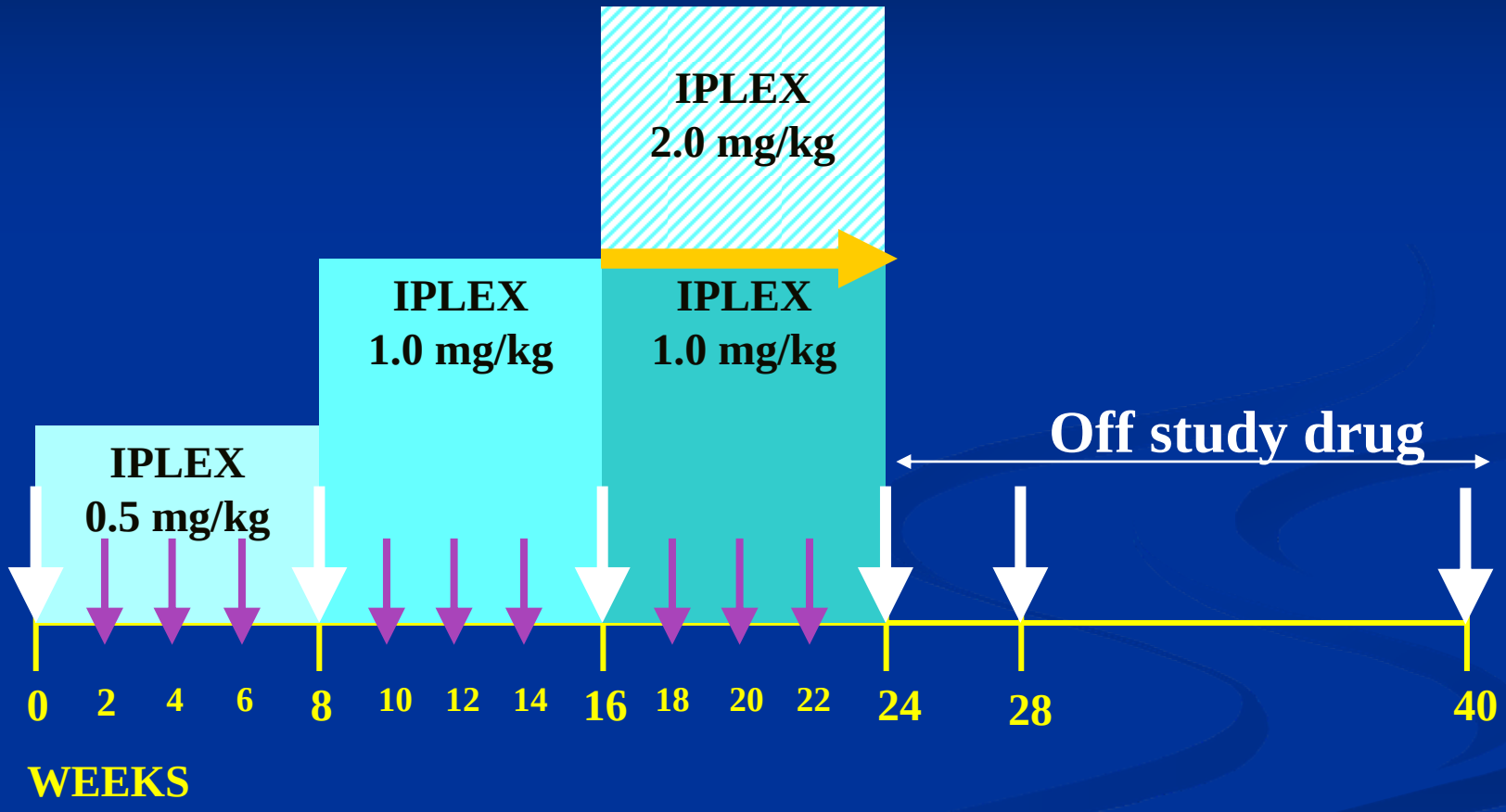
- Preparation of IGF-1 that may bypass insulin resistance and other anabolic defects that hamper muscle loss in DM1.

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

- **<u>Cohort 1</u>: 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.
- **<u>Cohort 2</u>: 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.

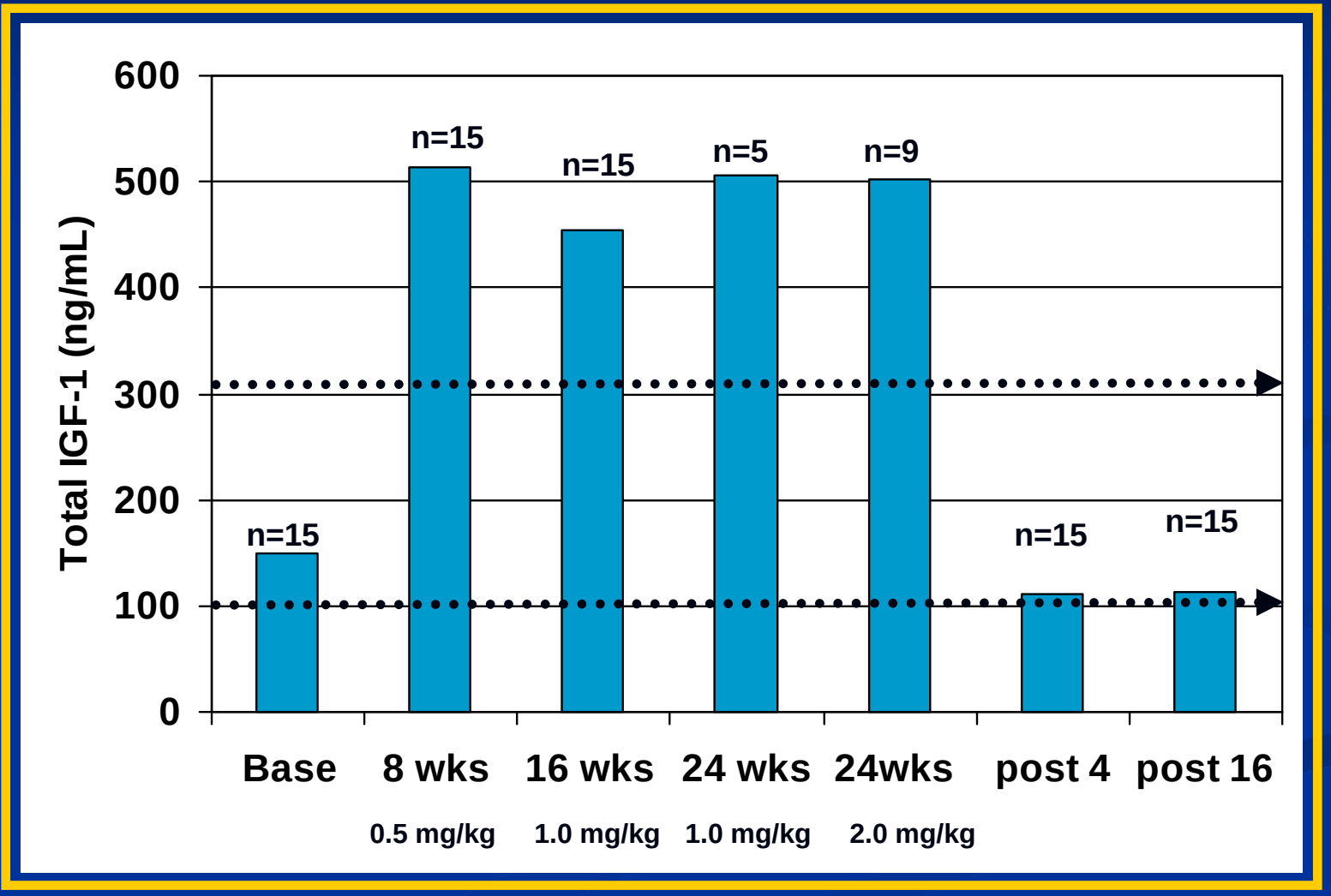
- 14 AEs probably related to study drug:
  - 2 AEs of light headedness,
  - 3 AEs of hypoglycemia,
  - 9 injection site reactions (n=8 patients).

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.

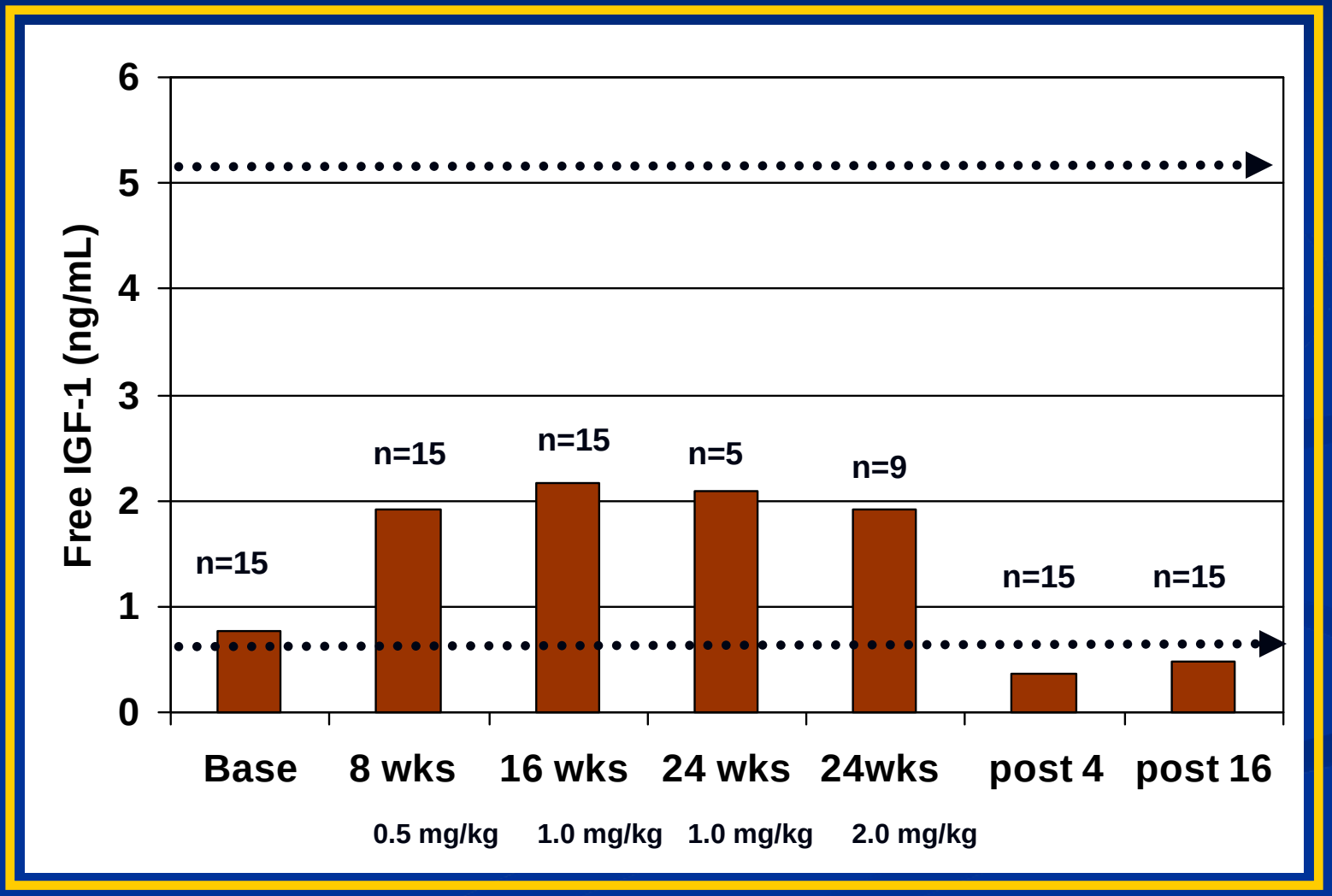
Total IGF-1 values

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



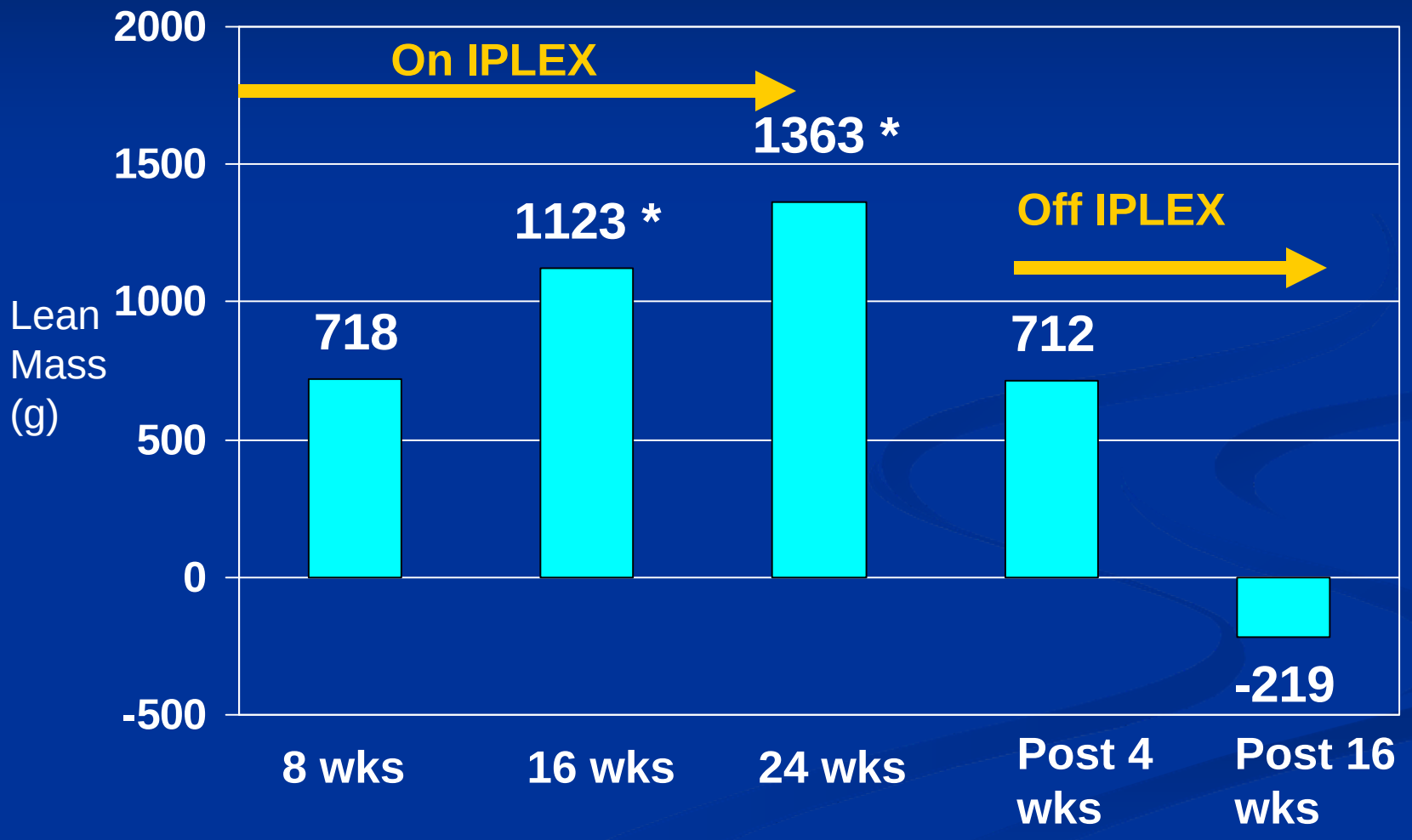
Free IGF-1 values

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).



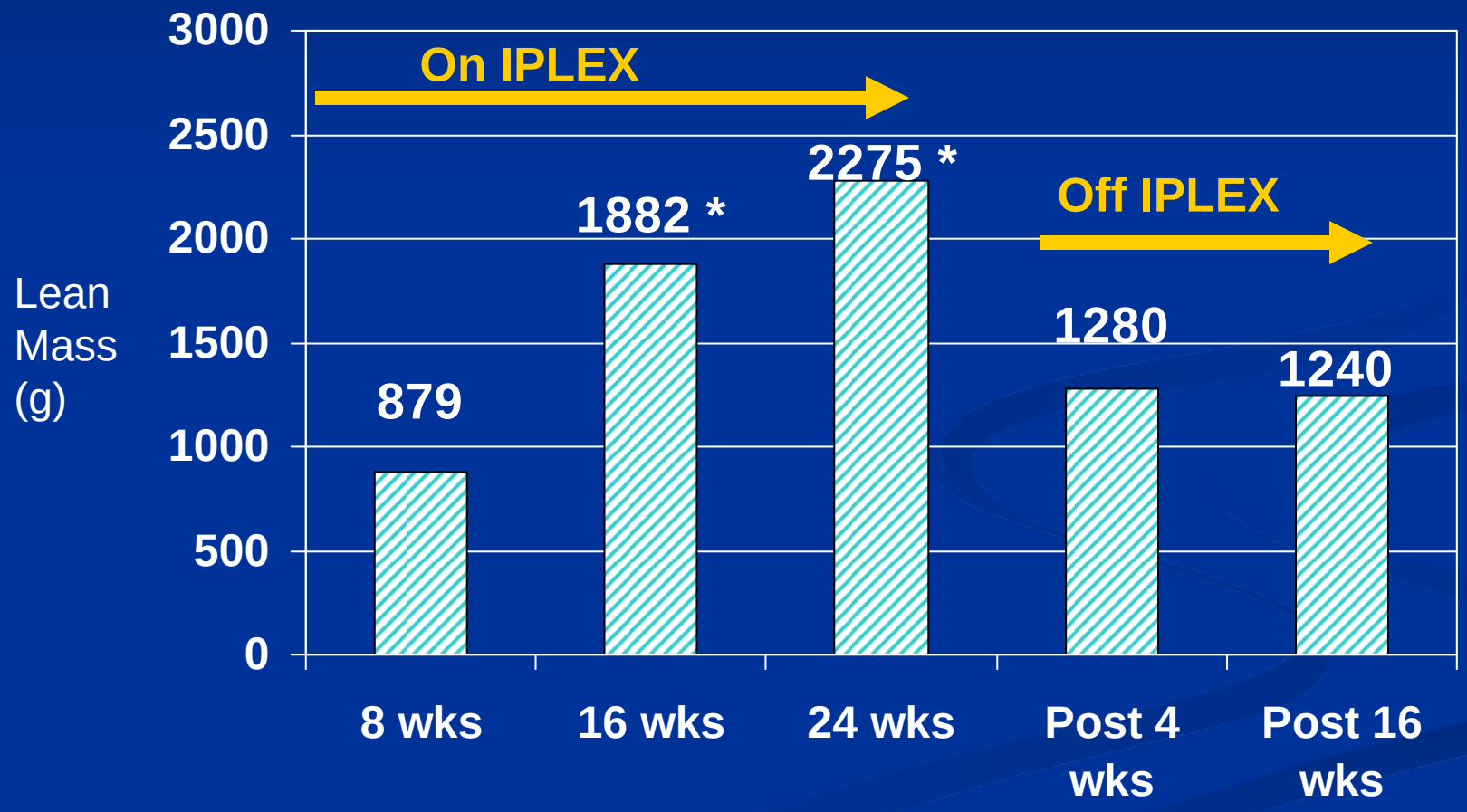
Lean Muscle Mass: Cohort 1

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

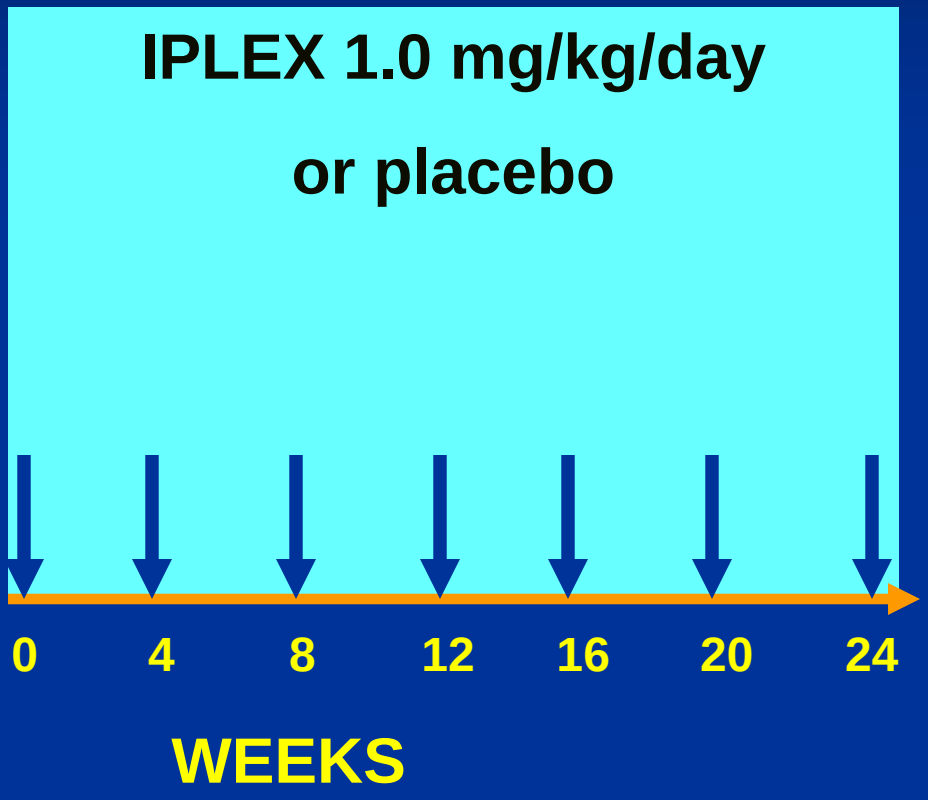
- These initial pilot studies have led to a multi-center collaborative study using methods established by our NIH Wellstone MDCRC dose escalation trial.

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?

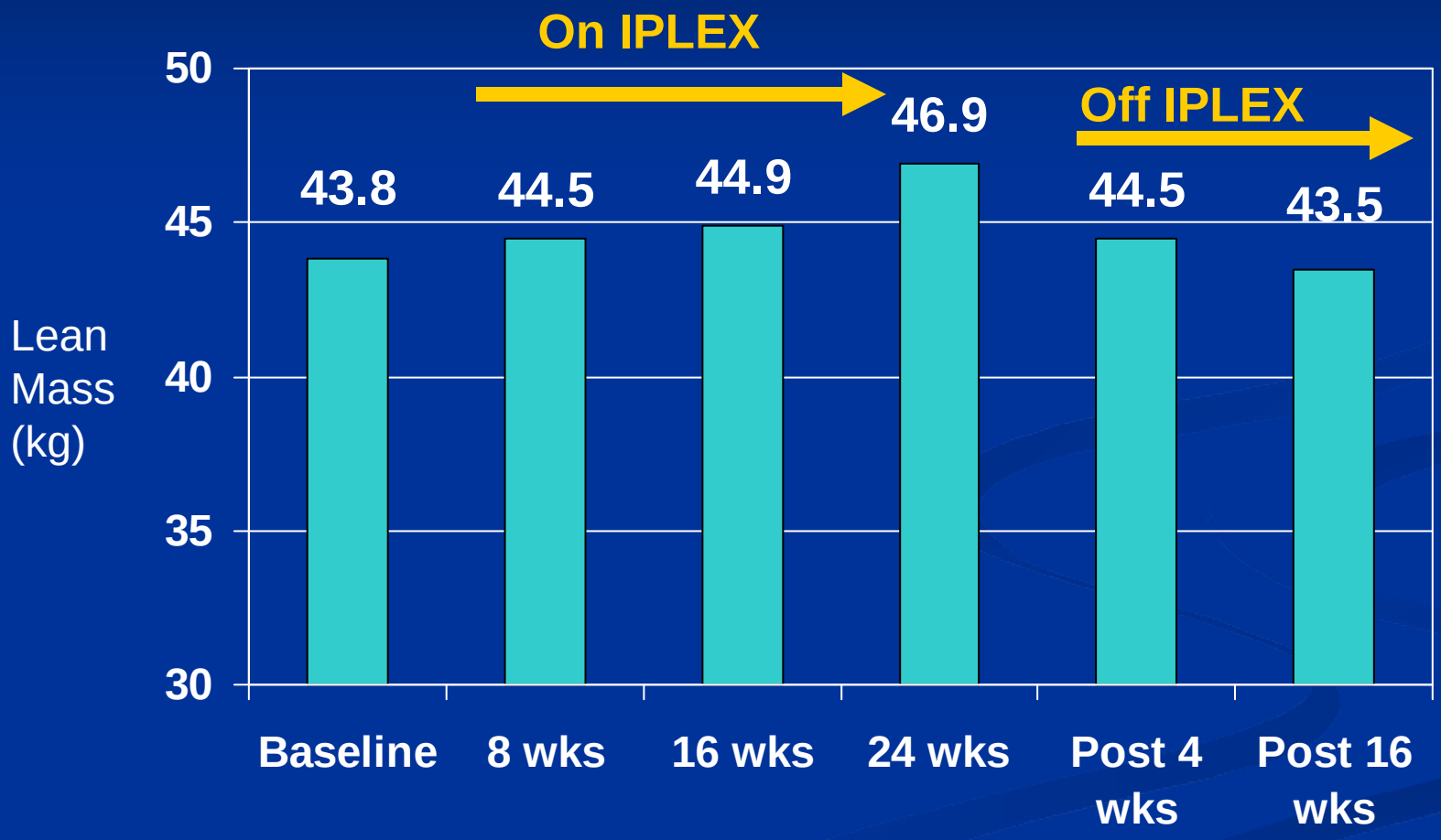
Future Questions

- 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).