

2014 Muscle Study Group Annual Scientific Meeting  
Challenges in Developing and Running Clinical Trials in  
Rare Diseases

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# Patient-Reported Outcomes (PROs) in Randomized Clinical Trials (RCTs)

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## Disclosures and Disclaimers

September 2014

- Non-executive director of Prana Biotechnology Ltd (Melbourne, Australia) as of May 12, 2014 – no stock options or equity positions
- Adamas Pharmaceuticals, Inc., American Academy of Neurology, Auspex Pharmaceuticals, AZTherapies, Banner Health/Genentech, Chelsea Therapeutics, Covington & Burlington LLP, Edison Pharmaceuticals, Genzyme, Isis Pharmaceuticals, JAMA Neurology, Lundbeck, Michael J Fox Foundation, NINDS (NeuroNEXT, PD Priorities), Orphazyme, Partners Health Care, Prana Biotechnology, Salamandra LLC, Seneb Biosciences, Sofinnova Venture Partners, University of California Irvine, Velocity Pharmaceutical Development, Voyager Therapeutics
- PI Georgetown U – FDA Center of Excellence for Regulatory Science & Innovation (CERSI - UO1 FD004319)
- *The views presented are those of Ira Shoulson and do not necessarily reflect those of the U.S. Food and Drug Administration*

# Patient-Reported Outcomes (PRO)

- General term that refers to self-reports by the patient
- Data may be collected by self-administered **questionnaires** completed by the patient or by **interviews** where the interviewer is gaining the patient's views – not where the interviewer uses patient responses to make a clinical assessment or judgment of the impact of the patient's condition.
- Patient perspective can play an important role in the approval of regulated medical products.

# PRO questionnaires assess:

- Symptoms (impairments) and other aspects of well-being
- Functioning (disability)
- Health status
- General health perceptions
- Quality of life (QoL)
- Health related quality of life (HRQoL)
- Reports and Ratings of health care.

# Patient-Centered Outcomes Research Institute (PCORI *JAMA* Aug 28, 2014).

- The evaluation of questions and outcomes that are meaningful and important to patients and caregivers
- As a condition for funding, PCORI requires engagement with patients and other relevant health care stakeholders in all of its funded research and views engagement in research as an important component of patient-centered research.
- PCOR makes sense, but its value has yet to be determined.

## **FDA Guidance for Industry (Dec 2009)**

### **Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims**

- Endpoint Model and Conceptual Framework
- Content and Other Validity
- Reliability, Ability to Detect Change
- Instrument Modification
- Instruments Intended for Specific Populations
  - children/adolescents
  - cognitively impaired ('we encourage observer reports that include only those events or behaviors that can be observed')
  - culture or language subgroups

**FDA Guidance for Industry (Dec 2009)**  
**Patient-Reported Outcome Measures: Use in Medical Product**  
**Development to Support Labeling Claims:**  
**Clinical Trial Design**

- Blinding and Randomization
- Quality Control
- Handling Missing Data
- Frequency of Assessments and Trial Duration
- Considerations for Multiple Endpoints
- Responder Definitions
- Electronic PRO Instruments
- Statistical Considerations

# The FDA CDER Drug Development Tools (DDT) Qualification Programs

- Clinical Outcome Assessments

## **Study Endpoints and Labeling**

**Development (SEALD)** Study Endpoints Team

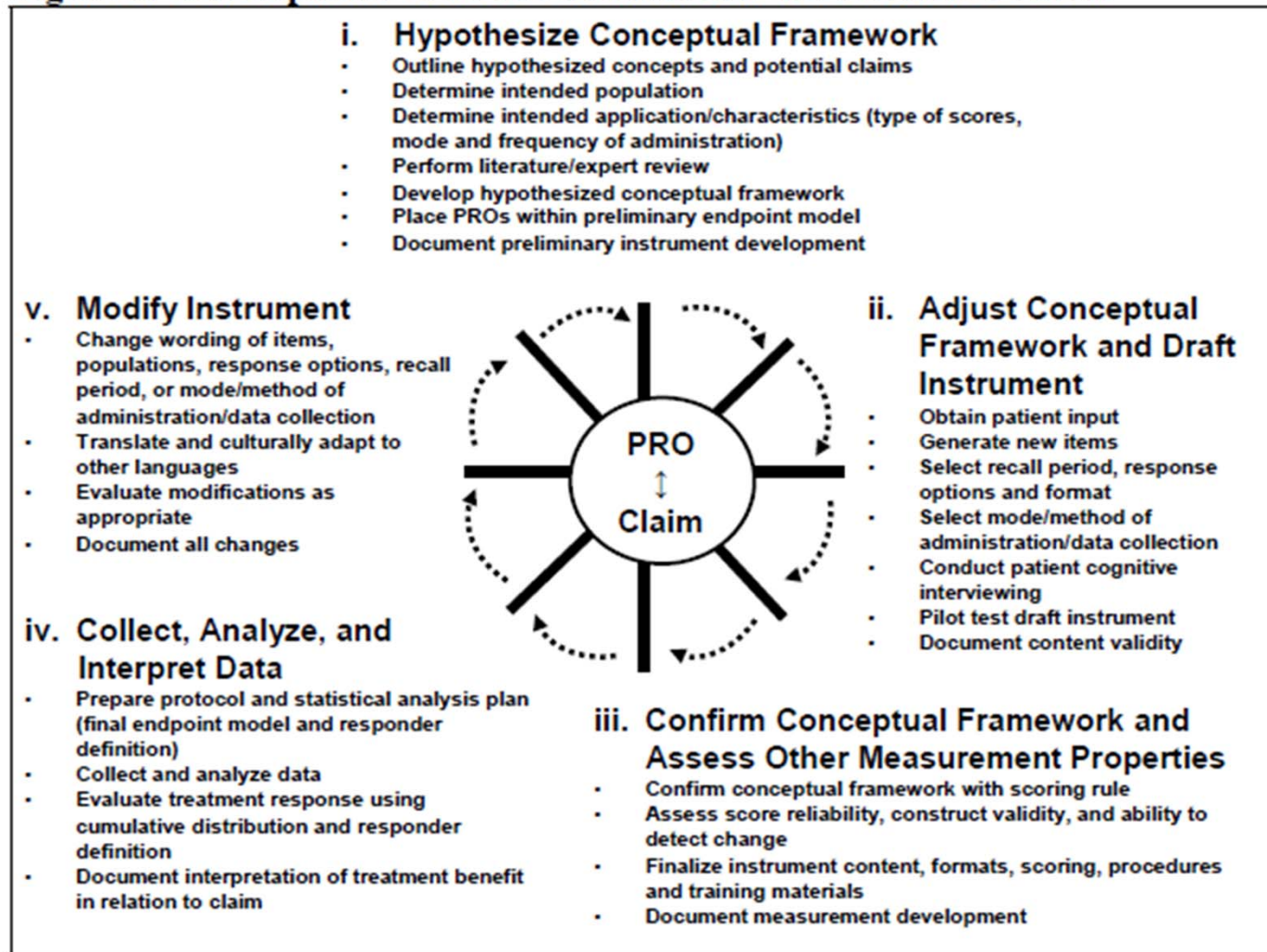
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- [CDER-BiomarkerQualificationProgram@fda.hhs.gov](mailto:CDER-BiomarkerQualificationProgram@fda.hhs.gov)
- [AnimalModelQualification@fda.hhs.gov](mailto:AnimalModelQualification@fda.hhs.gov)



**Figure 3. Development of a PRO Instrument: An Iterative Process**



DeMuro et al. Assessment of PRO label claims granted by the FDA as compared to the EMA.

*Value Health* 2013; 16(8):1150-5

- Reviewed drug approvals for the years 2006 - 2010.
- Of 75 drugs approved by both agencies, 35 (47%) had at least one PRO-related claim approved by the EMA compared to 14 (19%) for the FDA.
- The FDA was more likely to approve claims for symptom reduction, while the EMA approved relatively more claims for improvement in functioning or HrQoL.

# Patient-Reported Outcome of Problems (**PROP**)

- Simulate clinical care **interview** in clinical research ('problem list')
- Ask patients (subjects) what problem(s) bother them most (about their illness), and
- How it bothers them (the consequences)
- **Record verbatim**
- Categorize and analyze data independently
- Adapt and pilot in a RCT

# The HD-PROP

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- Keep it simple.
- What bothers you the most about your HD?  
How so?
- What bothers you the next most? How so?
- Compare prospectively baseline to subsequent visits.
- Compare prospective change according to randomized treatments (dosages).
- Look for signals in early-phase clinical trials.

# Huntington Disease Patient- Reported Outcome Problems (HD-PROP)

Piloting the HD-PROP in the  
HSG-Prana REACH2HD Clinical Trial

PI: Ray Dorsey MD

Co-PIs: Diana Rosas MD, Julie Stout PhD



# HD-PROP Questions asked:

- 1. What is the most bothersome problem for your Huntington disease?
- 2. In what way does this problem bother you by affecting your every day functioning or ability to accomplish what needs to be done?
- 3. How much (severely) does this problem bother you by limiting your functioning?

1 = Not at all

2 = Mildly (minimally or rarely)

3 = Moderately (more often than not)

4 = Severely (plenty or all of the time)



## Reach2HD

**1 4 2 HD PATIENT REPORTED OUTCOME PROBLEM ASSESSMENT (BL) 3 6**SUBJECT ID VISIT NO SITE NO VISIT  
DATE  DD  MMM  YYYY**Initial Assessment**

At entry into the study, please ask the Patient/Research Participant the following questions:

1. What is the most bothersome problem of your Huntington disease?  
(record the reply verbatim)  
  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_
2. In what way does this problem bother you by affecting your every day functioning or ability to accomplish what needs to be done?  
  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_
3. How much (severely) does this problem bother you by limiting your functioning? 3.   
1 = Not at all  
2 = Mildly (minimally or rarely)  
3 = Moderately (more often than not)  
4 = Severely (plenty or all the time)

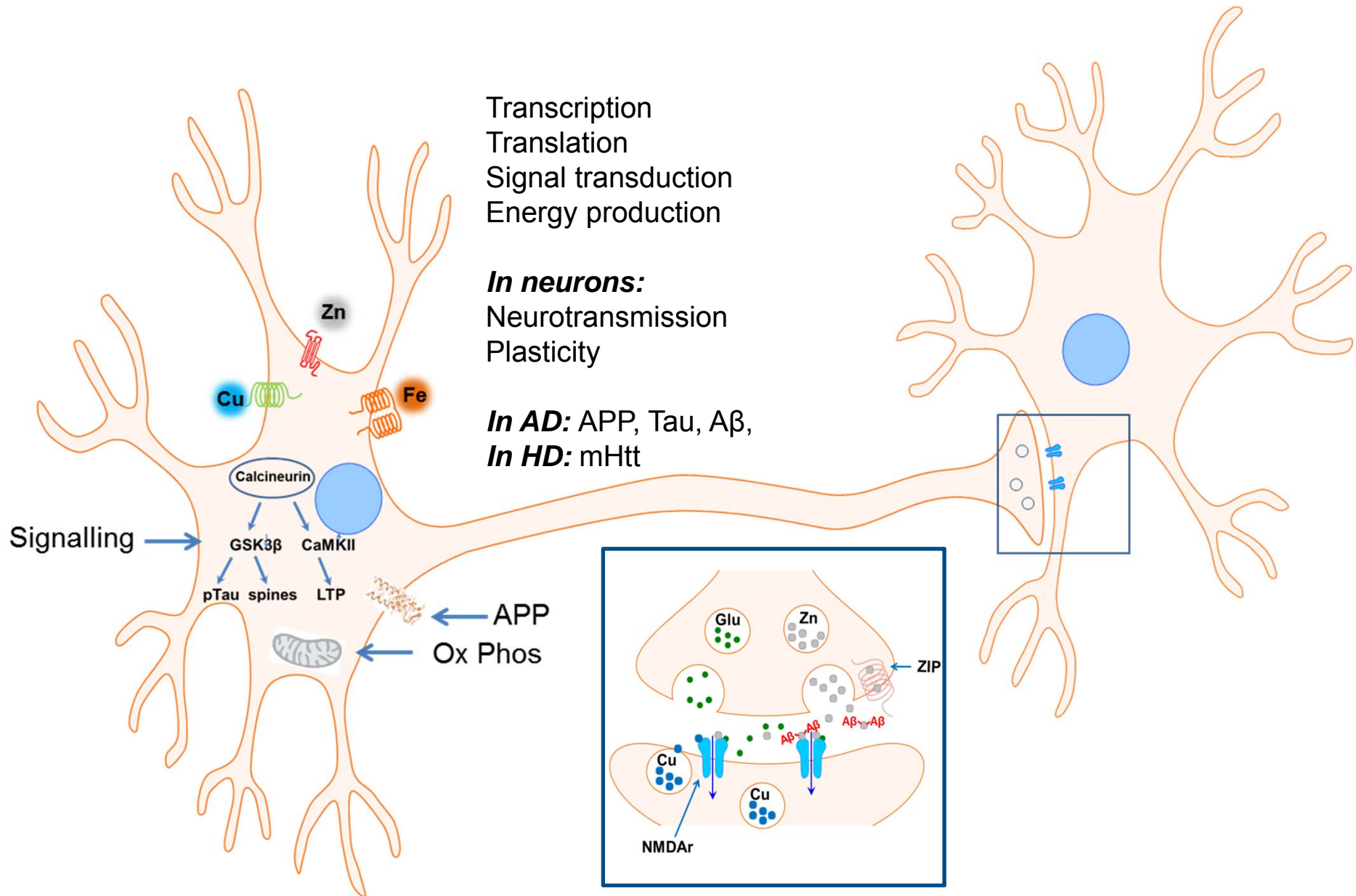


# REACH2HD Trial

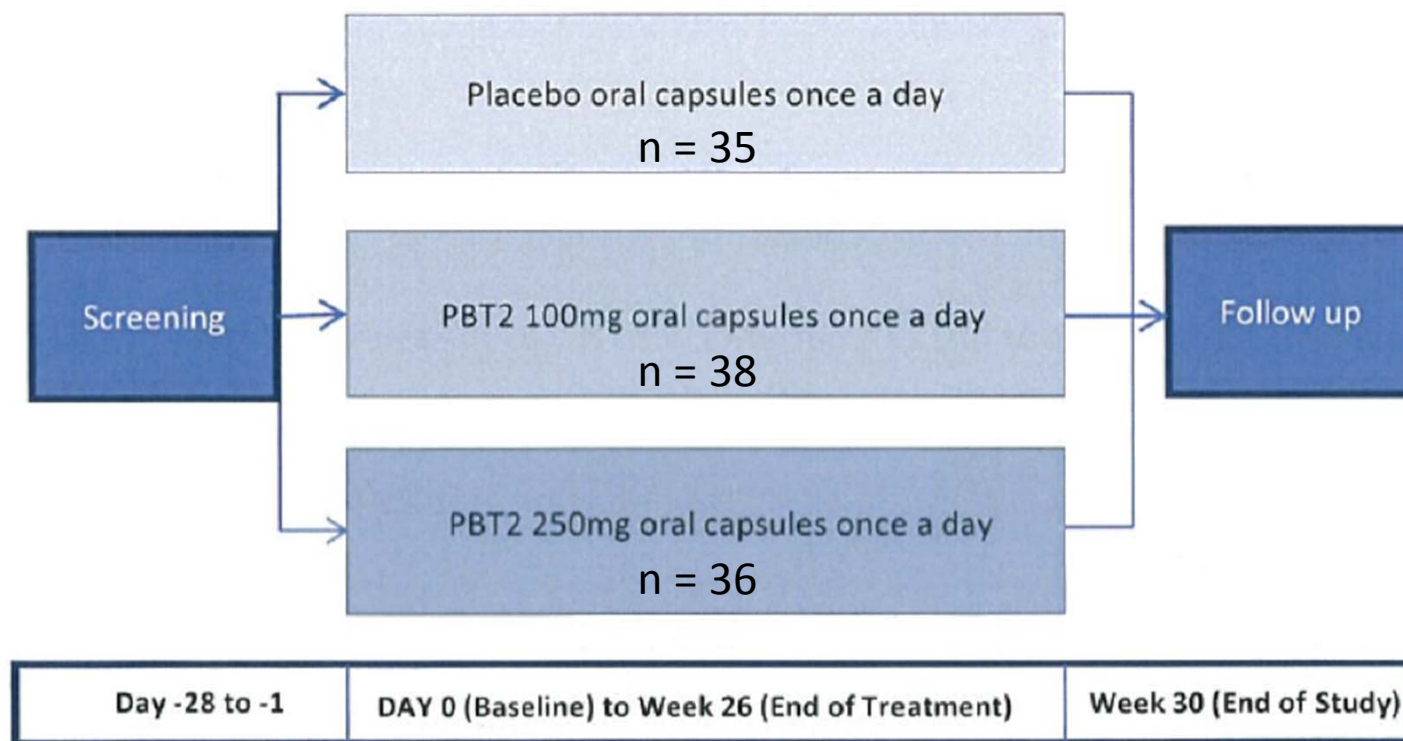
- Placebo controlled, double blind, randomized clinical trial
- Aim: examine safety and tolerability of PBT<sub>2</sub>, 100 mg/day and 250 mg/day, in early HD patients
- PBT<sub>2</sub>: favorably affects metal homeostasis in the brain  
-> improved cognitive function (in phase 2 AD trial)



# Metals Influence Major Cellular Activities



# Clinical Trial Design



HSG REACH2HD Investigators, ANA  
Poster # S451WIP, Oct 12, 2014, Baltimore MD

## PBT2 was well tolerated ...

### Tolerability

**PBT2  
250mg daily**

•32 (88.9%) of the 36 individuals randomized to PBT2 250mg completed the study

**PBT2  
100mg daily**

•38 (100%) of the 38 individuals randomized to PBT2 100mg completed the study

**Placebo**

•34 (97.1%) of the 35 individuals randomized to placebo completed the study

**Overall, 95% of participants  
completed the 26-week study**

## ... and generally safe in the study

### Safety of PBT2

#### **Serious adverse events**

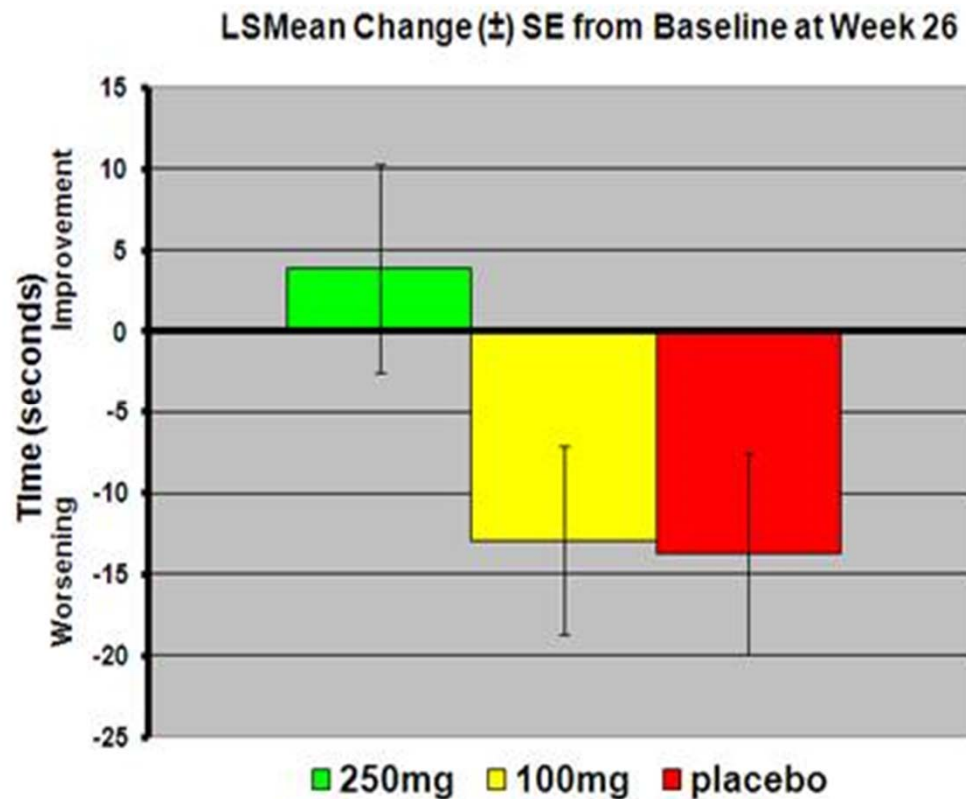
- Ten serious adverse events occurred during the study
- Nine were in the PBT2 groups (6 in PBT2 250mg; 3 in PBT2 100 mg)

#### **Adverse events**

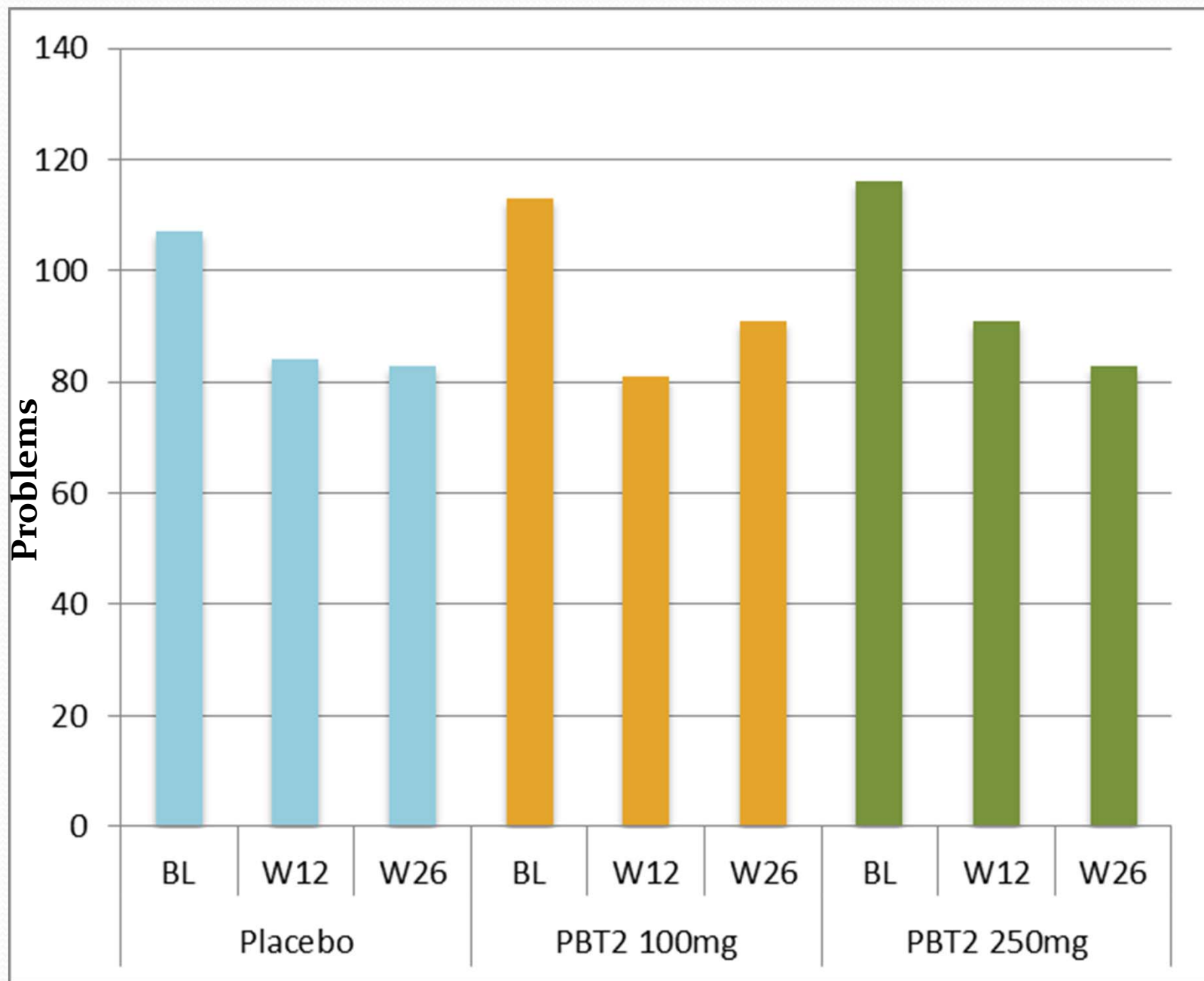
- Frequency of adverse events did not differ significantly across the three study groups
- Most common adverse events were diarrhea, headache, and falls, and the rates were similar across groups

# PBT2 250mg significantly improved performance on Trail Making Test Part B

## Change in Trail Making Test Part B



Improvement in Trail Making Test Part B was significant at 12 ( $p < 0.001$ ) and 26 weeks ( $p = 0.042$ )



**Figure 3.** Total number of problems reported, by Rx group.



# Examples- HD-PROP Responses

Problem Type	Example Quoted Patient Response
<b>Chorea</b>	Well, I guess the thing is not having control with my movements.
<b>Clumsiness</b>	I am getting a little more clumsy.
<b>Cognition</b>	Nothing – I am not aware that I have Huntington's – I am a little slow mentally.
<b>Memory</b>	My memory is not what I would like it to be. I struggle with names of relatives, acquaintances. I don't have any balance issues -- mostly memory and concentration.

# HD-PROP in REACH2HD

## Impressions

- HD-PROP shows how research participants identify and prioritize problems related to their HD
  - May be applicable to clinical trials
  - Characterizes unmet clinical needs
- Additional analyses underway to examine sensitivity and relationship to PBT2 effects
  - Functional consequences and severity of problems (scale 1-4)
  - Hierarchy of most bothersome problem reporting
- Piloted HD-PROP suggests need for comparisons with:
  - Clinic populations re geography/culture
  - Impact of cuing re prior responses
  - Paring of patient, caregiver and clinician reported treatment outcomes



# Overall HD Clinical Domain Impression

Clinical Global Impression (CGI) of Change

- How do you rate your abilities (change in) re:
  - coordination, balance, mobility...?
  - memory, concentration, multi-tasking...?
  - mood, outlook, nervousness...?
  - overall functions, activities...?
- Examine responses from research participants, caregivers and clinicians
- Compare with verbatim HD-PROP responses

# HD-PROP

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