Case Study:
Conduct of the Pediatric UC ENVISION Adalimumab Trial and Adolescents in an Adult Risankizumab Trial

Denise Schulz

Senior Director, Global Regulatory Strategy

AbbVie, Inc.

abbvie

Background: Humira (adalimumab) in Pediatrics

Humira (adalimumab) has been studied in 7 pediatric indications globally

- Juvenile Idiopathic Arthritis (JIA)
- Enthesitis-related Arthritis (ERA)
- Plaque Psoriasis (Ps)
- Hidradenitis Suppurativa (HS)
- Crohn's Disease (CD)
- Ulcerative Colitis (UC)
- Uveitis (UV)

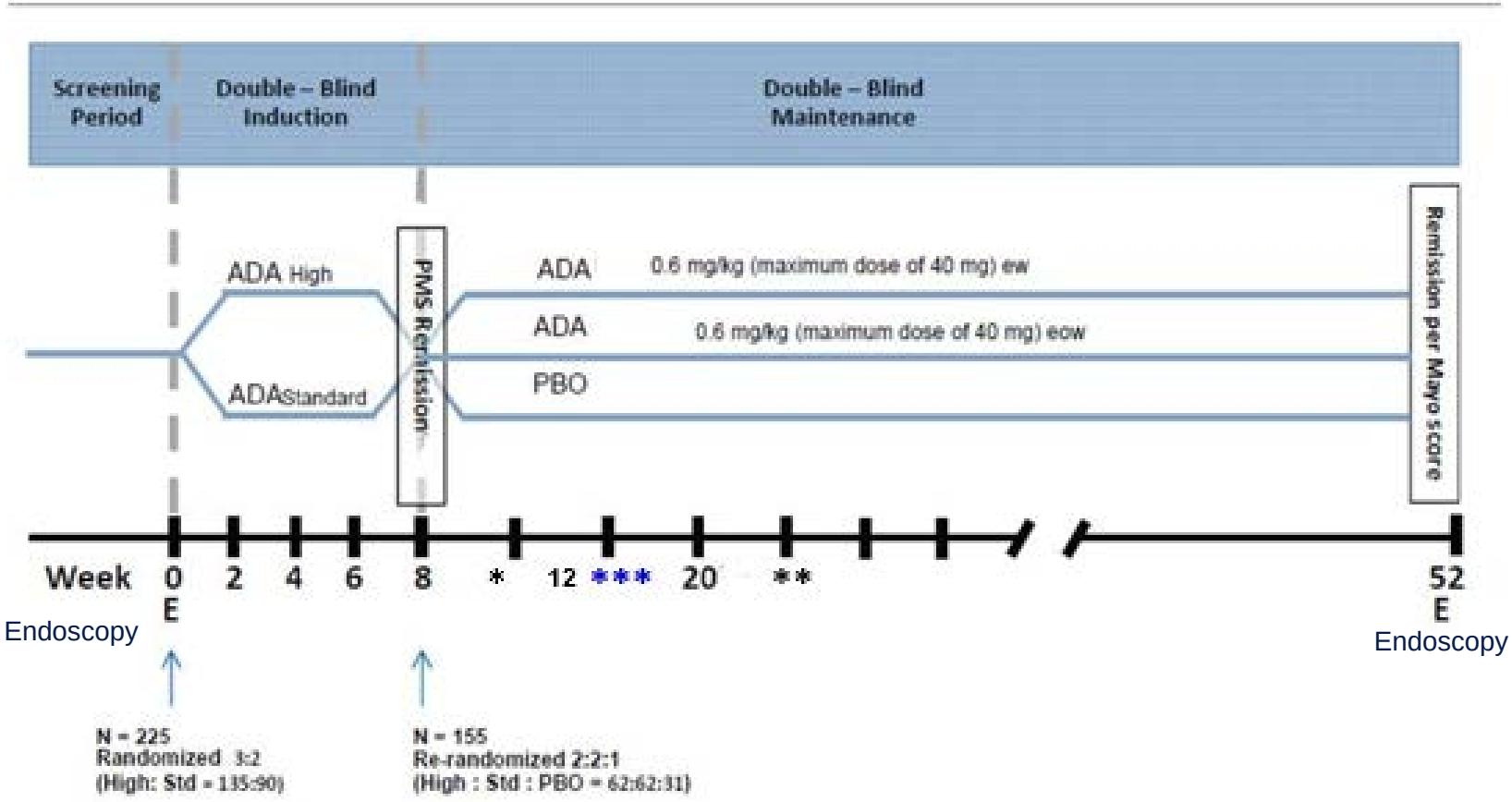
4 are approved in the US

- JIA
- HS
- CD
- UV

ENVISION Pediatric UC Study is ongoing in Ulcerative Colitis

- **2011:** FDA discussions on pediatric study began. FDA questioned the optimal dose of adult UC; No further discussions on pediatrics until adult UC approved. EMA required placebo.
- **2012:** Adult UC indication approved; PMR to study higher doses in adults
- **2013:** SPA followed by Type A meeting to discuss revised study; FDA agreed to pediatric study design with agreed to doses and endpoints followed by EU PIP modification

EMA & FDA: Agreed to Ped UC ENVISION Study Design



*	Re-Randomization of responders and discontinuation of non-responders at Week 8
**	Amendment 2: Loosened rescue therapy with active drug for flare at/after Week **20**
***	Amendment 3: Rescue therapy with active drug for flare at/after Week **12**

The Study: Barriers to Conduct and Enrollment

Placebo was a barrier for investigators, parents and study subjects

Infliximab was commercially available for pediatric UC

Adalimumab was commercially available in a pediatric formulation for pediatric CD and JIA in the US

Withdrawal of active treatment in UC patients with response (not remission) at Week 8 meant some patients could have residual disease

Worsening UC can lead to serious complications, including hospitalization and colectomy

Interruption of a biologic has theoretical immunogenicity concerns

The Study: Ped UC ENVISION Experience

220

Approximate number of sites approached; 100 declined study consideration (largely due to placebo arm)

Number of EU-5 countries (France, Germany, Italy, Spain, UK) that never had active sites; coordinating Investigators declined due to placebo arm

2

63

Number of sites activated across 15 countries; sites in 6 countries never enrolled a patient; 71% of patients enrolled were from Eastern Europe

Number of times we amended the protocol to reduce the screening and procedural burden, the criteria and time to qualify for active rescue treatment during the maintenance period to boost recruitment

(Amendment 4 in 2017 removed placebo after 2 years of negotiation with FDA and EMA's PDCO)

3

Other Barriers

Mg/kg dosing (requested by EU authority) added complexity

While the study was running, AbbVie was globally submitting and launching a new adalimumab formulation (100 mg/mL, without citrate buffers and less pain)

Global Harmonization of proposed amendments with FDA and EMA's PDCO took time; sometimes up to 6-10 months

Current Status: Ped UC ENVISION Study

2018

Agreement to

- Cease enrollment and follow subjects to completion of study
- Use external placebo

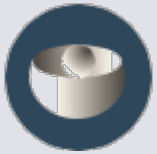
2019

Requested Type B meeting; granted 125 days from meeting request date

The study is still ongoing 8 years after first FDA interaction

Pivotal Trials: A note on enrollment of adolescents….

For risankizumab Phase 3 CD program, AbbVie proposed enrollment of 16 and 17-year-olds “where locally permissible”



EU Committee for Medicinal Products for Human Use (CHMP) requested full physical maturity for these subjects

Some countries have not approved the protocol (outright) for the reason of including these subjects, leading to delays in study start-up in some geographies

Adolescent enrollment commenced 8 months ago; 5 adolescents have enrolled

Closing Comments

- Placebo is a major problem in pediatric IBD programs; even when it was acceptable to investigators, it is not for parents/patients

- Extrapolation, trials with unblinded comparators, or external placebo controls deserves strong consideration as innovative trial designs by regulators to accelerate the conduct of pediatric trials

- Although AbbVie has been successful in the removal of placebo in ENVISION, other subsequent IBD pediatric plans have received comments back by Agencies requiring placebo

- Negotiation currently occurs separately with both EMA PDCO and FDA
  - There is a need for more collaboration and lessons learned by Agencies from previous trials
  - There is a need for an agile mechanism for Dual Agency Meetings to facilitate global harmonization of clinical development programs

Acknowledgements

- Thank you to the investigators and study sites who have participated in our clinical trials

- We would especially like to thank the parents and children who have been willing to consider participation