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Lessons Learned in the Conduct of a Pediatric IBD Trial: ENVISION

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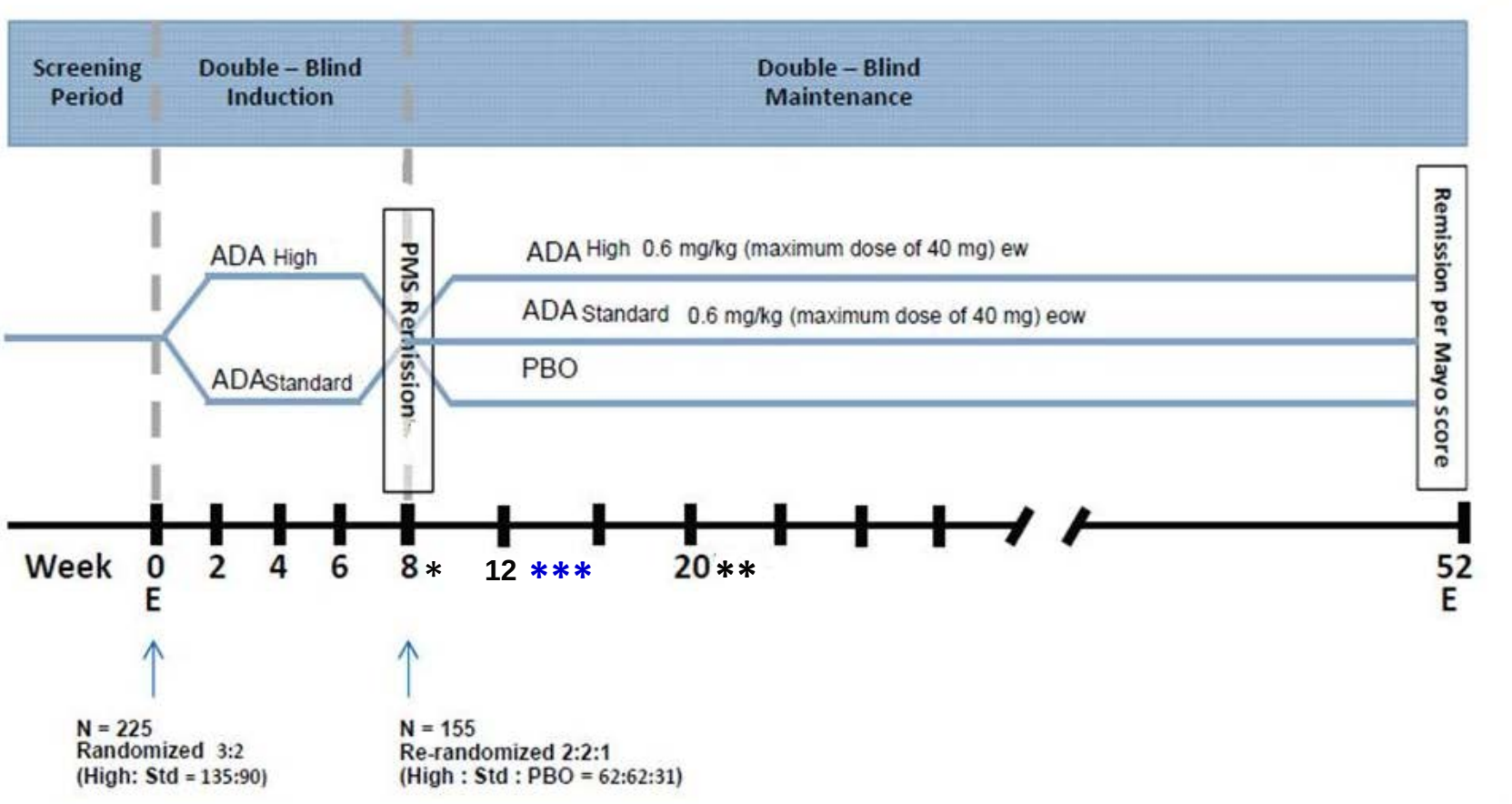
ENVISION (adalimumab pediatric UC study) background

Issues with the adalimumab adult UC program complicated the pediatric program

- Dose-response curve in the adult program was not shouldered; “optimal” induction dose not identified
- Led to a FDA PMR for another adult study (ongoing) to evaluate higher induction and maintenance doses
- Limited the extrapolation to pediatrics that could be done with the existing adult data

Original 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**

Placebo was a problem

Infliximab was already commercially available for pediatric UC

Adalimumab was already commercially available in a pediatric formulation for pediatric CD

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

ENVISION experience (ex-Japan)

Approximately 220 sites were approached; 100 declined study consideration (largely due to placebo arm)

Two EU5 countries (France and Germany) never had active sites

- Coordinating Investigators declined due to placebo arm

63 sites were activated in 15 countries

- Sites in 6 countries never enrolled a patient

We amended the protocol 3 times to reduce the screening and procedural burden, and criteria and time to qualify for active rescue treatment during the maintenance period in an effort to boost recruitment

- Amendment 4 removed placebo, after agreement from FDA and PDCO

Enrollment data: 48 months later

71% enrolled patients are from Poland; 13% from US

Overall enrollment rate: 0.04/patients/site/month

Year	Sites active	Enrollment Rate
2015	47	0.050
2016	46	0.036
2017	41	0.044
2018 (reflective of placebo removal)	36	0.058

Other issues

Mg/kg dosing (requested by EU authority) added complexity, study visits, and contributed to several at-home dosing errors

Too many visits (12 in 52 weeks; 6 in first 8 weeks)

AbbVie launched a new formulation of adalimumab (100 mg/mL, without citrate buffers) while the study was running

ePRO technology changed since the trial began (large, clunky devices became outdated)

Daily diary compliance declined over time (perhaps diary entries could have been prescribed just during the days prior to the visit)

Lessons learned

The adult program affects the pediatric program

Placebo is a major problem in pediatric IBD programs

- Even when it was acceptable to investigators, it was not for parents/patients

Not sure there is a “work around” for the placebo problem outside of extrapolation

- Longer induction period and re-randomizing only patients with remission prolongs trial and increases sample size in a rare disease

We need to get creative in looking at ways to limit travel and other burden on subjects (e.g., remote data collection), but this does not mitigate the fact that pediatric IBD is a rare disease and therefore studies in this disease will enroll slowly

A note on enrollment of adolescents in pivotal trials

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

CHMP requested full physical maturity for these subjects

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

Enrollment of adolescents has not yet commenced, so we do not yet know if the inclusion of the placebo arm in the studies will limit the enrollment of these adolescent subjects

Acknowledgements

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

We’d especially like to thank the parents and children who have been willing to consider participation