September 17, 2024

Robert M. Califf, MD
Commissioner
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Submitted at regulations.gov

Re: FDA-2024-D-2682 — Pediatric Inflammatory Bowel Disease: Developing Drugs for Treatment; Draft Guidance for Industry; Availability

Dear Dr. Califf:

The undersigned organizations representing pediatric patients with inflammatory bowel disease (IBD) and the physicians who care for them appreciate the opportunity to comment on the Food and Drug Administration's (FDA) draft industry guidance for developing drugs for treatment of pediatric IBD as published in the *Federal Register* on July 19, 2024.

Biologic and other advanced therapies have significantly improved clinical outcomes and the quality of life[1,2,3] for those affected by IBD, including Crohn's disease (CD) and ulcerative colitis (UC). Unfortunately, while more than a dozen agents have been approved for adults with IBD, pediatric patients with IBD are negatively affected by the lack of indications for all but two biologic agents.[4] Consequently, physicians spend hours per week dedicated to fighting insurance denials to treat their patients with these therapies.[5,6,7] Insurance companies leverage the absence of pediatric indications or the lack of labeling of pediatric-appropriate dosing to deny access for children with IBD to effectively-dosed advanced therapies.[8]

This draft guidance constitutes an important recognition that extrapolation of efficacy from adequate, well-controlled trials of adult subjects is reasonable for pediatric patients who have the same clinical indications. Understanding age-related effects on pharmacokinetics (PK) and pharmacodynamics (PD) remains vital.[9,10,11,12,13,14,15] Therefore, **we ask the FDA and industry to focus on early phase PK/PD studies to establish dosing across a range of ages and weights, especially for children less than 30 kg in body weight.** In addition, while adult data can be used to extrapolate efficacy and early safety, it is critical to establish and employ long-term safety registries to assure true pediatric safety.

We appreciate the FDA extending the offer to comment on the draft guidance and giving this opportunity to advocate for a new path, as the current paradigm has yielded only two approved agents for pediatric IBD over a quarter century's time. Early phase PK/PD trials, extrapolation of efficacy and long-term safety registries would provide effective, new treatment opportunities for pediatric patients. In addition to this vital advocacy for a paradigm change, our organizations offer the following comments in response to FDA's specific suggestions and recommendations about the attributes of clinical studies being developed for the treatment of pediatric UC or CD.

DEVELOPMENT PROGRAM

Study Population

FDA Recommendation: Subjects should have a confirmed diagnosis of pediatric UC or CD based on documented findings on endoscopy and histopathology.

We agree on the need for a firm diagnosis in all research subjects. We also point out that children with IBD have a higher likelihood of being diagnosed with "unclassified" IBD (IBD-U) and not a confirmed diagnosis of UC or CD. IBD-U is used for the diagnosis when a physician cannot differentiate between UC or CD. IBD-U is an important subgroup of IBD. When industry aims to recruit patients with very early onset IBD (VEO-IBD), the population of potential study participants will be significantly limited by excluding patients with IBD-U from the study population.[16,17,18,19]

Our organizations recommend that in addition to documented findings based on upper and lower endoscopy and histopathology, small intestine imaging should be included when establishing a diagnosis of CD.[20]

FDA Recommendation: For pediatric UC, the recommended approach is to use the same criteria to define disease activity and endpoints in pediatric subjects as in adult subjects (i.e., the modified Mayo Score (mMS)).

Our organizations recommend that the Pediatric Ulcerative Colitis Activity Index (PUCAI),[21,22] an instrument validated for measuring disease activity in children and adolescents with UC, be considered as an alternative to the modified Mayo Scoring (mMS) for assessing pediatric UC activity and severity, and treatment response.

FDA Recommendation: For drugs intended to treat moderately to severely active pediatric UC or CD, sponsors should enroll pediatric subjects across the whole range of disease severity categories.

Biological plausibility should be considered. For instance, the majority of pediatric patients with IBD have moderate-to-severe disease activity at diagnosis making it not clear how industry would fulfill the FDA's recommendation of enrollment of pediatric patients "across the whole range of disease severity."

FDA Recommendation: For drugs intended to treat moderately to severely active pediatric UC or CD, sponsors should enroll pediatric subjects who reflect the characteristics of clinically relevant populations, including with regard to race and ethnicity, and should consider clinical study sites that include higher proportions of racial and ethnic minorities to recruit a diverse study population.

This is a very laudable objective, and while we enthusiastically support diverse inclusion, pediatric studies of IBD are unlikely to include large study populations. Restricting recruitment to only medical centers with diverse populations will limit recruitment for a low-incidence disease,[23,24] and lead to smaller sample size. Our societies have demonstrated the ability to recruit diverse populations by including a diversity of medical centers and practices. For example, the recent COMBINE[25] trial recruited a more diverse population of pediatric patients than all prior pediatric IBD trials.

FDA Recommendation: FDA encourages the inclusion of adolescent subjects (subjects 12 to 17 years of age inclusive) in adult CD or UC clinical trials, provided that preliminary safety and efficacy data in adult subjects support enrollment. FDA encourages sponsors to discuss the proposed sample size of adolescent subjects with the appropriate review division at the time of protocol development.

Our organizations urge caution when considering the inclusion of adolescent subjects in adult CD or UC trials because of potential PK/PD differences,[26,27,28,29] especially given that pediatric IBD patients can suffer from being significantly underweight.[30,31] If adolescent subjects (12 to 17 years of age) are included in adult CD or UC clinical trials, and provided that preliminary safety and efficacy data in adult subjects support enrollment, there should be clear expectations of the number of enrollees in the adolescent age group that would be required to gain regulatory approval for a drug or biologic for use in that age group. For example, trials for rizankizumab included subjects down to the age of 16 years;[32] yet, approval was not granted down to this age group. This recommendation should be clarified to encourage

enrollment targets for the 12 to 17 years-of-age cohort in adult clinical trials. Further, if trials include adolescents, then approval should include the age group evaluated in the study.

Study Design

FDA Recommendation: Sponsors developing drugs for the treatment of pediatric UC or CD should consider a randomized, double-blind study that evaluates at least two dose levels for each age and/or weight cohort, respectively.

Our organizations ask the FDA to explain the rationale for mandating relatively small, randomized, double-blind studies with at least two dose arms. As noted earlier in our comments, extrapolation of efficacy from adult studies paired with both PK/PD dose finding studies performed before adult approval and with long-term, post-approval registries would be more informative and clinically relevant.

Our organizations appreciate FDA's recognition that when a therapeutic agent already has adult approval, the risks of randomizing pediatric subjects with active disease (at risk of disease worsening and complications) to placebo will outweigh the potential benefits of study enrollment.[33,34,35] The risks of non-treatment make it very difficult to recruit pediatric subjects to a study that randomizes subjects with active disease to placebo.[36] FDA does not explicitly advise against using a pediatric placebo arm, but which should be added to the guidance. Further, non-treatment of children with a treatable disease (i.e., treating with placebo) is unethical and should not be allowed in pediatric IBD trials.[37]

Additionally, if different dose levels are implemented, both dose arms must be expected to be efficacious based on PK/PD or other preliminary studies. Use of sub-therapeutic doses is inappropriate, since under-treatment is as unethical as non-treatment.

FDA Recommendation: Dose selection for pediatric studies should be guided by a well-characterized dose/exposure-response relationship in adult subjects for the same indication.

Children weighing less than 30kg on average need higher per-kg dosing than adults, as shown for all monoclonal biologics thus far (adalimumab, infliximab, vedolizumab, mirikizumab, and golimumab). The single pediatric study[38] on the use of adalimumab in pediatric patients with moderate-to-severe UC indicated that children may require twice the adult dosing. This study predicts that immunoglobulin-based biologics may have different pharmacokinetics in pediatric patients with IBD than in adults and support the real-life observations that pediatric patients commonly need significant dose intensification of these drugs compared to historical FDA guidance on dosing. Therefore, we believe this strategy risks the creation of study arms with suboptimal dosing which will not only hamper study enrollment but are not ethical and reinforce the need for meaningful, early-phase PK/PD studies.

EFFICACY CONSIDERATIONS

Efficacy Assessments

FDA Recommendation: Maintenance of remission.

Our organizations object to three endoscopic evaluations (at enrollment, week 8, and week 52). There is no discussion of the added value of the 8-week colonoscopy. Presumably this is to evaluate for induction treatment response. We suggest an 8-week colonoscopy is a notable deterrent to patients (and their families) who may be interested in study participation but unwilling to have an endoscopy prior to the start of the trial and again at week 8. This requirement also ignores the real psychological effect of colonoscopy clean-out on pediatric patients with IBD, including anxiety, and medical trauma/stress, not to mention the risks associated with additional sedation.

Our organizations recommend limiting the number of endoscopies to a maximum of two, one at baseline and one at the end of the study (52 weeks). A third post-induction colonoscopy or flexible sigmoidoscopy would be optional. For CD, non-invasive assessments, such as magnetic resonance enterography, intestinal ultrasound and fecal inflammatory markers, could be used to supplement pediatric Crohn's disease activity index (PCDAI) scores.[39] In UC, the PUCAI and fecal inflammatory markers have a very strong correlation with treatment response.[40,41]

FDA Recommendation: For pediatric UC efficacy assessment, FDA recommends that sponsors use colonoscopy to document disease activity in all involved segments of the colon.

Our organizations support the use of colonoscopy for pediatric UC efficacy assessment, but the FDA should revise its recommendations to limit the number of endoscopies to a maximum of two per study (one at baseline and one at the end of the study). As mentioned above, a post-induction colonoscopy or flexible sigmoidoscopy could remain optional.

FDA Recommendation: As secondary endpoints for pediatric UC efficacy assessment, FDA recommends corticosteroid-free remission, and specifically pediatric subjects who are in clinical remission (defined by the mMS) at the conclusion of the study (e.g., 52 weeks) and have no corticosteroid exposure during a pre-specified period (e.g., at least 8 to 12 weeks) before that assessment.

We ask that FDA clarify in its guidance whether its recommendation is intended to include budesonide with regard to the definition of corticosteroid free.

SAFETY CONSIDERATIONS

FDA Recommendation: FDA has previously recommended a washout period for prior therapies of five half-lives, or an undetectable serum level (when available). To promote timely enrollment of pediatric subjects with active disease, reduce the potential need for escalation of corticosteroids as bridging therapy, and reduce the potential loss of study eligibility, sponsors may propose shorter washout periods, with appropriate justification.

While we appreciate FDA's suggestion that sponsors may propose shorter washout periods with "appropriate justification," washout periods are the most significant barrier to enrolling pediatric patients, especially those with worsening disease activity who are at risk of adverse outcomes, including hospitalization, surgery, and use of steroids. A washout period of five half-lives can simply be too long, especially when patients are sick and, due to rapid drug clearance in this population, does not have biologic basis.[42,43,44]

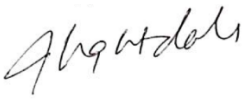
Study sponsors should have the opportunity to design a study without a washout period, which reflects common clinical scenarios in which patients who are not responding to a treatment may need to be moved to another treatment without a full washout period.[45] Delay in initiating therapy is associated with increased risk of worsening disease outcomes.[46,47,48] We appreciate that in lieu of a washout period, FDA recommends an undetectable serum level, but as the FDA recommendation notes, serum levels cannot be measured for all therapies such as small molecules and, when available, may not be covered by payers and insurance companies. In addition, if a child has active disease in the presence of detectable serum drug level, that therapy is demonstrably ineffective. Trials should be designed to enable enrolling without a washout period, as long as the risk of the study drug is not considered to be substantially increased. This would be more representative of real world practice and would be more acceptable to parents. Requiring a sick child to undergo a washout period necessitates a period of non-treatment, and substantially increases the risk of adverse disease outcomes. This is both a significant barrier to recruitment for families, and, as noted above, represents an unethical period of non-treatment of a child with a treatable disease.[49]

CONCLUSION

Our societies thank you in advance for consideration of our concerns and recommendations. **While we appreciate the opportunity to comment on the FDA's proposed recommended guidance for prospective randomized control trials, we want to conclude by emphasizing that early phase PK/PD trials, extrapolation of efficacy from adult studies and long-term safety registries offer opportunity to improve treatment options for pediatric patients with IBD. We therefore respectfully urge the FDA to shift its guidance in this direction.**

Questions or requests for additional information should be directed to Camille Bonta, NASPGHAN policy advisor, at cbonta@summithealthconsulting.com or (202) 320-3658.

Sincerely,



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