

Inclusion of Adolescents With Adults in Phase 3 Clinical Trials: Overview of the Current State and a Call for Action

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Current Paradigm for Drug Development in Adolescents

The primary objective of drug development from industry and regulatory perspectives is to enable patients' access to safe and efficacious treatments in a timely manner. This objective is typically achieved through demonstrating efficacy and safety of novel pharmacological compounds in pivotal clinical trials.¹ Currently, if a disease occurs in both pediatric and adult populations, a drug to treat such disease is usually evaluated first in adult phase 3 clinical trials before clinical trials are initiated in the pediatric population. Adolescent patients (defined here as 12 to <18 years old) are typically included within the pediatric trials, which take place after completion of adult trials. This approach leads to delay in the access of adolescents to efficacious treatments by many years after approval in adult patients for the same condition, as shown for some examples in Table 1. This lag in drug approval often leads to off-label use in adolescents of drugs approved for treatment of adult patients, resulting in missed opportunities to collect efficacy and safety data in adolescent patients, and can expose patients to medications that may not be optimally safe or efficacious.²

Patients younger than 18 years old are often excluded from phase 3 trials in adults partly because optimal drug doses and formulations are expected to be different between pediatric and adult patients, which necessitates confirming the optimal adult doses in phase 3 studies before enrolling pediatric patients. Although differences in dosing and formulation between adults and pediatrics are generally more relevant to children <12 years of age, they do not necessarily apply to adolescents. For adolescents in many cases there is no significant physiological basis to suggest different efficacy or safety profiles from adults; hence, similar doses and formulations for adolescents (with certain body weight cutoffs) and adults are often recommended for the same condition (Table 1). This similarity in approved doses between adolescent and adult patients

is not surprising given that drug disposition pathways (renal elimination, hepatic metabolism, or transport) reach the adult activity levels by age of 12 years, and the pharmacodynamics is generally similar between the two age groups.^{3–7}

In the United States, the Additional Safeguards for Children in Clinical Investigations (21 CFR 50 Subpart D) provide a regulatory and ethical framework that can be used to gauge the appropriateness of enrolling adolescents with adults in phase 3 trials,⁸ and further guidance on the timing of initiation of pediatric studies is provided in the Pediatric Research Equity Act guidance.⁹ Under 21 CFR 50.52, adolescents can be included in clinical trials if (1) the risk is justified by the anticipated benefit to the subjects, (2) the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches, and (3) adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians. Therefore, if data are available in adult patients from well-conducted phase 2 trials, these data can be used to assess the benefit versus risk of including adolescents with adults in phase 3 to enable timely availability of new treatments to adolescents. In such cases, modeling and simulation approaches can be valuable to inform the expected

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Table 1. Examples of Drug Approvals by FDA and Dosing Recommendations in Adults and Adolescents^a

Drug	Condition	Approval in Adults	Approval in Adolescents	Dose in Adolescents and Adults
Harvoni (ledipasvir)	Hepatitis C virus	2014	2017	Same dose in adults and adolescents ≥ 35 kg
Latuda (lurasidone)	Major depressive episodes with bipolar disorder	2013	2018	Adults: starting dose 20 mg QD; maintenance dose 20-120 mg QD Adolescents: same starting dose; maintenance dose 20-80 mg QD
Sovaldi (sofosbuvir)	Hepatitis C virus genotypes 2 and 3	2013	2017	Same dose in adults and adolescents ≥ 35 kg
Gilenya (fingolimod)	Relapsing multiple sclerosis	2010	2018	Same dose in adults and adolescents > 40 kg
Stelara (ustekinumab)	Plaque psoriasis	2009	2017	Same dose in adults and adolescents ≥ 60 kg
Lithium	Bipolar I disorder	1980	2018	Same dose in adults and pediatrics > 30 kg

FDA indicates US Food and Drug administration; QD, once daily.

^aSource: Drugs@FDA. <https://www.accessdata.fda.gov/scripts/cder/daff/>.

Table 2. Challenges and Mitigation Strategies for Inclusion of Adolescents in Clinical Trials

Challenge	Possible Mitigation Strategy
<ul style="list-style-type: none"> • A perceived lack of clear regulatory path for drug approval in adolescents even if they were included with adults in phase 3 trials. • Potential delay in the completion of phase 3 trials if a predetermined minimum number of adolescents need to be enrolled. • Need for additional investigating sites in addition to sites where adult patients are enrolled and location of the proper sites to recruit adolescents among pediatric and adult care healthcare service points. • Ethical, legal, and logistical barriers with respect to obtaining assent/consent from adolescents and their guardians, particularly when the clinical trial is related to sexual and reproductive health or involves the use of contraception. 	<ul style="list-style-type: none"> • Discussions between the sponsors and regulatory agencies before starting phase 3 trials to ensure alignment on the path for potential approval of the developed drug in both adolescents and adults. • Although enrollment of an adequate number of patients may be necessary to ensure the benefit-risk profile of a drug to support drug use in adolescents in addition to adults, there is no general regulatory mandate specifying a minimum number of adolescents who need to be included in a phase 3 study. • The adequacy of the number of adolescents in a clinical trial can potentially be demonstrated based on similarity of the proportions of adolescents in the trial and in the overall target population. • Conducting studies at research institutions where both adolescents and adults are treated (eg, research departments within academic institutions/hospitals). • Collaborations between adult and pediatric patient sites including, where feasible, facilitated ethical approval. • Inclusion of pediatric experts on study steering and safety-monitoring committees and as study principal coinvestigators. • Involvement of community and adolescents themselves in the design and ethical approval of the clinical trials aimed at this population.¹⁵

plasma exposures and clinical response in adolescents based on models developed in adults.¹⁰

Challenges for Inclusion of Adolescents With Adults in Phase 3 Trials and Possible Mitigation Strategies

There are a number of challenges (perceived or real) that limit the ability and willingness of sponsors to include adolescents with adults in phase 3 trials, which typically stem from differences between adolescent and adult patients in psychosocial, ethical, and social aspects as well as from the capacity to independently access and enroll in the clinical trials. These challenges and potential mitigation strategies based on

lessons learned from adolescent studies in different diseases¹¹⁻¹⁴ are summarized in Table 2.

A Paradigm Shift: Recent Examples of Concurrent Enrollment of Adolescents and Adults in Phase 3 Trials

Because of the complexity of involving adolescents in clinical trials, it is important to identify and learn from successful strategies that led to proactive involvement of adolescents into adult phase 3 clinical trials. Several drugs have been approved by the US Food and Drug Administration (FDA) for treatment of adults and adolescents when adolescents were included with adults in phase 3 trials (Table 3). In some other instances (eg, the fixed dose combination [elvitegravir, cobicistat,

Table 3. Examples of Recently Approved Drugs That Included Adolescents With Adults in Phase 3 Trials

Approved Drug	Disease	Age, Weight Cutoff ^a	Adults/Adolescents in Phase 3 Trials Presented in US Prescribing Information
Orkambi (lumacaftor and ivacaftor) ²⁴	Cystic fibrosis	12 years	908/340
Nucala (mepolizumab) ²⁵	Severe asthma	12 years	683/28
Xofluza (baloxavir marboxil) ²⁶	Acute uncomplicated influenza	12 years, 40 Kg	1318/118
Symdeko (tezacaftor-ivacaftor) ^{27,28}	Cystic fibrosis	12 years	729/187
Moxidectin ²⁹	Onchocerciasis	12 years	1393/79
Takhzyro (lanadelumab-flyo) ³⁰	Hereditary angioedema	12 years	115/10

^aAge and weight cutoff values from the US Prescribing Information from the original drug approval (lower age/weight may have been approved in subsequent applications).

emtricitabine, and tenofovir alafenamide] and dolutegravir), open-label studies in adolescents were conducted separately in parallel to the adult phase 3 randomized controlled trials, which enabled concurrent approval in adult and adolescent patients.^{16,17} The FDA has recently issued draft guidance on Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials, including oncology trials that are earlier than phase 3.¹⁸ Therefore, it is anticipated that there will be an increasing number of oncology clinical trials in the near future that enroll adolescents with adults in clinical trials. It is worth noting that many of the considerations for including adolescents in oncology trials in the FDA guidance (eg, assessing similarity of disease between adult and pediatric patients, dosing considerations, safety monitoring, and ethical considerations) can also be relevant to non-oncology phase 3 trials. Additionally, a number of non-oncology phase 3 trials are currently ongoing that enroll both adults and adolescents with inflammatory diseases,^{19,20} psychiatric disorders,²¹ infectious diseases,²² and hematologic diseases,²³ among others.

Conclusions and a Call for Action

The majority of current adult phase 3 trials exclude subjects younger than 18 years of age. As a result, adolescents are often grouped in a stepwise approach with younger children (<12 years old) in post-adult approval clinical trials, leading to a missed opportunity for adolescents to have access to safe and efficacious new drugs simultaneously with adults. Despite the complexities and challenges for enrolling adolescents with adults in phase 3 trials, there is evidence to support a paradigm shift.

In order to enable availability of treatments for adolescents at the same time as adults, pharmaceutical companies are requested to evaluate the potential for including adolescents with adults in phase 3 trials when (1) the disease is a continuum between adults

and adolescents with no known significant differences in pharmacodynamic responses, disease prognosis, or manifestations; (2) the pharmacokinetics of the drug has been characterized in adult patients and is expected to be similar between adolescents and adults (which can be informed with confidence using modeling and simulation approaches); and (3) efficacy and safety data generated in adult patients (e.g. in Phase 2 trials) support that the potential benefits to adolescents outweigh the risks of inclusion in the Phase 3 clinical trials. Sponsors will need to discuss with regulatory agencies prior to embarking on a Phase 3 trials that include adolescents to ensure adequacy of the studies conducted to support potential approval for use in both adult and adolescent patients. The end-of-phase-2 meeting presents the best opportunity to do so.

Additionally, it is imperative that all stakeholders (pharmaceutical companies, regulators, ethics committees, scientific and medical societies, and patient advocacy groups) collaborate to address the challenges to inclusion of adolescents in clinical trials highlighted herein in order to facilitate the evaluation of new treatments in adolescents simultaneously with adults.¹⁵ These discussions should occur early on in the development process so that all factors are considered and discussed with regulators well before phase 3 studies are initiated. Stakeholders should foster educational and advocacy opportunities to increase the peer and public involvement, discuss the pharmacological bases for combining adolescents with adults in phase 3 trials, and further address the ethical considerations of this approach. Finally, a harmonized regulatory guidance for non-oncology drugs is necessary to help inform the level of evidence required to be generated in phase 3 studies to support approval of treatments in patients 12 years and older in a timely manner.

In summary, there is a missed opportunity in the current drug development paradigm for enabling timely availability of efficacious treatments for adolescents. Enrollment of adolescents with adults in phase 3 trials

should be considered based on understanding of their development, both physiologically and psychosocially, and through assessment of the risks and benefits of including them in clinical trials.¹¹ It is important to find the delicate balance among accelerating access of adolescents to new medications, minimizing off-label use, and increasing our understanding of the safety and efficacy of new treatments in adolescents while avoiding potential delay to drug development programs in adults.

Conflicts of Interest

Dr. Mohamed is an employee and shareholder of AbbVie. Dr. Rakhmanina and Dr. Hassan report no relevant disclosures.

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