

Pediatric Extrapolation in Type 2 Diabetes: Future Implications of a Workshop

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Extrapolation from adults to youth with type 2 diabetes (T2D) is challenged by differences in disease progression and manifestation. This manuscript presents the results of a mock-team workshop focused on examining the typical team-based decision process used to propose a pediatric development plan for T2D addressing the viability of extrapolation. The workshop was held at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) in Orlando, Florida on March 21, 2018.

BACKGROUND

To market a drug, sponsors must demonstrate the effectiveness and safety of their products usually through the conduct of adequately powered and well-controlled studies in the target patient population. In the case of pediatric drug development, industry often must rely to some extent on extrapolation. Pediatric extrapolation is a concept that integrates available knowledge, and identifies critical gaps and uncertainties in that knowledge, to subsequently define a targeted set of required clinical data to fill the knowledge gaps. When extrapolation is justified, a wide spectrum of approaches and study designs may be acceptable and it may be merely based on pharmacokinetic (PK) and exposure matching to support conclusion of efficacy in the pediatric population.

For youth with type 2 diabetes (T2D), pediatric clinical development plans usually include two major components: A pharmacokinetic and pharmacodynamic (PK–PD) study or substudy to support dosing and administration recommendations for each relevant pediatric subpopulation, and one confirmatory pivotal clinical trial designed to establish the product's safety and efficacy in children and adolescents.¹ A similar PK–PD relationship between adults and pediatrics has been demonstrated for some classes of oral antidiabetics from short-term studies.² However, long-term studies have demonstrated greater insulin resistance, higher insulin secretion, and more rapid loss of β -cell function and glycemic control in youth when compared with adults.^{3–6} The observations in youth with T2DM suggesting differences in pathogenesis of disease suggest that response to treatment in short-term PK–PD studies may provide limited evidence to support dose selection for confirmatory clinical trials in youth and adults.

To explore the use of extrapolation in product development for youth with T2D as a potential path, a workshop was held as part of a preconference at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) in Orlando, Florida on March 21, 2018, cosponsored by the pediatric working group (PWG) of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) and the special population group at ASCPT. The workshop highlighted a case example and included a mock project-team environment involving key expertise from academia, industry, and regulatory agencies. The use of model-informed drug development (MIDD), efficient innovative analytics, and strategic collaborative approaches were discussed. Some information in this manuscript was neither presented nor discussed at the mock-team discussion but rather resulted from follow-up discussions among the authors of this manuscript.

REGULATORY FRAMEWORK IN PEDIATRIC PRODUCT DEVELOPMENT

In the European Union (EU) and the United States (US), the passage of important legislation has increased the availability of pediatric-specific information in drug labeling. In the European Union, the Paediatric Regulation includes both incentives and requirements. In the United States, the Best Pharmaceuticals for Children Act provides an incentive and the Pediatric Research Equity Act⁷ provides a requirement to conduct pediatric studies.

The EU Paediatric Regulation requires medicines to have a pediatric investigation plan (PIP), not later than upon completion of the human pharmacokinetic studies in adults. The PIP is aimed at ensuring that the necessary data obtained are of high quality

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and ethically researched to support authorization in children. All applications for marketing authorization for new medicines must include the results of studies as defined in the PIP, unless a waiver or deferral has been granted. Similarly, in the United States, a pediatric study plan is required under Pediatric Research Equity Act, no later than the end of phase II.⁷ The PIP and the pediatric study plan can usually be aligned supporting a common, global pediatric development program. Based on data collected from the first 10 years of the Paediatric Regulation and since the implementation of the legal framework in the United States, these legislative initiatives have been successful in increasing the availability of approved therapies for pediatric patients in several areas, but the needs in other areas such as T2D remain to be addressed.⁸

The US Food and Drug Administration (FDA), European Medicines Agency (EMA), and National Medical Products Administration (NMPA) have adopted the International Council for Harmonization (ICH) Guideline: E11 (R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population. This guideline includes considerations related to the use of pediatric extrapolation in pediatric medicines development.⁹ In October 2018, the EMA also published the final version of its reflection paper to provide guidance on the use of extrapolation in the development of medicines for pediatrics.¹⁰

The EMA framework is allowing flexibility and context-dependent approaches for how different types of prior knowledge could be used to support assumptions or make predictions for proposed pediatric studies or entire development programs.¹¹ The reflection paper encourages high-quality study planning and design to be addressed early in the pediatric development planning by generating an extrapolation concept and extrapolation plan as part of the pediatric strategy and plan. This should lead ultimately to a more targeted generation of evidence ensuring that children only participate in clinical trials with specific objectives that further support the scientific understanding of a medicinal product for use in children and address the requirements for regulatory decision making. The NMPA follows guidance from ICH, EMA, and the FDA published guidance on extrapolation using prior information, such as adult data.^{12,13}

The FDA, EMA, and NMPA^{14,15} have also published specific guidance related to development of drugs for T2D, including recommendations for pediatric development from the FDA and EMA.^{14,15} The EMA guidance, published in 2012, recommends that pediatric patients 10–18 years of age be studied. However, EMA recommends, in general, that separate pediatric trials should be conducted, and that the timing of pediatric studies should follow ICH E11 guidance. The EMA guidance also does not recommend that studies in children be initiated before sufficient safety and efficacy data from adult trials are available.¹⁴ The FDA draft guidance on drug development for T2D, published in 2008, which includes a discussion of pediatric drug development is less specific about age groups to be studied and the timing of such studies.¹⁵ However, in general, as discussed during the workshop, the FDA has also recommended that pediatric patients 10–18 years of age be studied^{16,17} and that, in general, separate pediatric trials should be conducted that follow ICH E11 guidance. Sponsors of products being developed for pediatric T2D should be assured that regulators are striving to harmonize

the approach to pediatric T2D drug development, including addressing the extent to which efficacy can be extrapolated from adult data. Despite the considerable alignment between the EMA and FDA in the regulatory framework for pediatric therapeutics development, sometimes differences are identified for which alignment may help facilitate the efficiency of pediatric studies. To this point, regulators created the Pediatric Cluster in 2007, a forum that allows informal exchange of scientific information and discussion of specific product development issues as they arise, to avoid delays in product development. This Cluster now includes the FDA and the EMA, as well as Pharmaceuticals and Medical Devices Agency (Japan), Health Canada, and Therapeutic Goods Administration (Australia). The FDA and EMA continue to harmonize on scientific issues pertaining to pediatric product development through at least monthly discussions of the Pediatric Cluster. In a recent review, it was shown that the FDA and EMA have converged approaches for 73% of the issues discussed (368/507) with respect to the development of over 100 products in the past 3 years.¹⁸

PEDIATRIC EXTRAPOLATION IN YOUTH-ONSET T2D: CASE STUDY

The workshop highlighted a case example that included discussions on disease manifestation and progression, some background information on the hypothetical compound, and considerations for clinical programs.

Disease manifestation and progression

An overview of the key differences between adults and youth with T2D in terms of epidemiology and pathophysiology is depicted in **Table 1**.

Table 1 Youth-onset and adult-onset T2D: similarities and differences

	Youth	Adult
Epidemiology		
US incidence	~5,000/year	~1.5 M/year
US prevalence	~ 35–50,000	~ 25 M
Sex ratio (M:F)	1:2	1:1
Risk factors		
	Obesity	Obesity
	Ethnicity	Ethnicity
	Low socioeconomic status	Low socioeconomic status
	Puberty	Puberty
	Exposure to diabetes during pregnancy	Exposure to diabetes during pregnancy
	Parental diabetes	Parental diabetes
Pathophysiology		
Prediabetes	Definition unclear, may be transient	Prolonged prodrome
Insulin resistance	Severe	Mild to severe
Insulin secretion	Initially hyperresponsive and then rapid loss	Progressive loss
Treatment	Higher rate of failure	Lower rate of failure

US, United States.

Epidemiology. Youth-onset T2D occurs most often during the second decade of life, with a median age of diagnosis of 13.5 years,¹⁹ coinciding with the peak of physiologic pubertal insulin resistance; youth-onset T2D rarely occurs prior to puberty. While the disorder occurs in all races, there is a much greater prevalence in populations at overall high risk for T2D, such as American Indians, Africans and African-Americans, Latinos, East and South Asians, Indigenous Australians, and Pacific Islanders. Nearly all youth with T2D have a body mass index (BMI) above 85th percentile for age and sex, with the median BMI > 99th percentile, and come from populations characterized by low socioeconomic and educational status, likely a consequence of many factors, including metabolic characteristics, cultural/environmental influences, and quality of access to health care. Interestingly, youth-onset T2D has a sex disparity, such that 2/3 of adolescents with T2D are female, whereas there is no such sex difference in the incidence of T2D in adults,¹⁹ further supporting an association with hormonal changes of puberty.

Pathophysiology. Glucose homeostasis is maintained by a balance between insulin secretion from the pancreatic β -cells and sensitivity to insulin in the periphery.²⁰ When insulin sensitivity declines, insulin secretion must increase to maintain glucose tolerance and, in most circumstances, decreased insulin sensitivity is adequately compensated by increased insulin secretion. However, when β -cells cannot secrete insulin sufficiently to compensate for insulin resistance, abnormalities in glucose homeostasis ensue, potentially progressing to prediabetes and T2D as β -cell function deteriorates further.²⁰ Studies in youth with obesity and increasing degrees of dysglycemia from normoglycemia to prediabetes to T2D show, as in adults, that β -cell failure is the underlying pathophysiologic phenomenon.²¹ During puberty, insulin sensitivity decreases 25–30% in healthy adolescents.²² In the presence of functioning β -cells, puberty-related physiologic insulin resistance is adequately compensated by increased insulin secretion and normoglycemia is maintained. However, in adolescents with obesity, there is a further 50% decrease in peripheral insulin sensitivity, and the individual who has maintained adequate β -cell compensation for obesity-associated insulin resistance prior to puberty may not be able to further compensate for the added insulin resistance that accompanies entry into puberty, raising the risk for development of worsening dysglycemia during the transition. Of interest, this close association with puberty is also likely responsible for another unique feature of youth-onset T2D, namely the phenomenon of regression to normoglycemia that occurs with exit from puberty in 30–60% of youth with prediabetes and T2D.²³

Evidence also suggests that maternal obesity and gestational diabetes mellitus (GDM) contribute to T2D in youth. In the Treatment Options for T2D in Adolescents and Youth (TODAY) cohort, one third were born after a pregnancy complicated by preexisting diabetes or GDM.²⁴ In the SEARCH for Diabetes in Youth study, exposure to maternal diabetes and maternal obesity were independently associated with T2D in adolescents.²⁵ Age of onset of T2D was also younger in those exposed to GDM. Data from TODAY has indicated that youth with T2D born following exposure to maternal diabetes had lower insulin secretion than their peers who did not have this exposure.²⁶

Insulin resistance in youth appears to be much greater than in similarly obese adults. Data from the Restoring Insulin Secretion (RISE) Study have shown that clamp-derived insulin sensitivity in obese youth with prediabetes or recent onset T2D is 50% that of BMI-matched adults with a similar degree of dysglycemia. Furthermore, insulin secretion was 2–3 times higher in youth than in BMI and glycemia matched adults^{5,6} and is disproportionate to the degree of insulin resistance, suggesting that β -cell hyperresponsiveness may be characteristic of the process in youth.

Available data suggest that deterioration in glycemic control is more rapid in adolescents than reported in adults. In the TODAY study, loss of glycemic control occurred in just under 50% of participants on metformin monotherapy by 36 months, compared with approximately 10% of adults on metformin monotherapy in A Diabetes Outcome Progression Trial (ADOPT).^{4,27} This increased rate of loss of glycemic control is associated with a more rapid decline in β -cell function in TODAY than in adults in ADOPT.^{4,27} The more rapid loss of β -cell function in youth has recently been confirmed by direct comparison of changes in β -cell function in youth and adults in the RISE Study.²⁸

In summary, while T2D in adults and youth share the underlying pathophysiology of insulin resistance and progressively inadequate β -cell compensation to demand, youth have greater insulin resistance, hyperresponsiveness of insulin secretion, and more rapid loss of β -cell function and glycemic control than adults. On the other hand, there is also a higher rate of reversion to normoglycemia, with or without intervention, in some youth as they exit puberty. These differences represent key determinants of dosing requirements in general and likewise need to be considered in the use of extrapolation to support pediatric T2D drug development.

Pharmacology and clinical response to treatment

The hypothetical compound was defined as an oral antidiabetic drug in the sodium/glucose cotransporter 2 inhibitor (SGLT2i) class with a development in adults currently at end of phase II. The pediatric indication targets add-on therapy to metformin in youth-onset T2D (10 to 18 years of age). As a primary mechanism of action, the SGLT2i compound blocks the SGLT2 protein that is involved in 90% of glucose reabsorption in the proximal renal tubule, resulting in increased urinary glucose excretion and lower serum glucose. An overview of the expected age-related differences in pharmacology and clinical response for this specific class is depicted in **Table 2**.

General considerations for clinical programs

Efficacy of T2D products in adults is usually established in at least two double-blind, placebo-controlled multicenter clinical trials evaluating the effect of the product on the change in hemoglobin A1c (HbA1c) from baseline vs. the change in HbA1c in the placebo control group, typically after 6 months of treatment. As well as representing the direct clinical benefit of treating symptomatic hyperglycemia, reduction in HbA1c is a surrogate for microvascular disease risk reduction and reflects a weighted average of ambient blood glucose levels over the previous 8 to 12 weeks. Efficacy in youth with T2D is typically established with only one adequate and well-controlled clinical trial in pediatric patients aged 10 and older,

Table 2 Overview of pharmacology and clinical response to treatment of the hypothetical compound

Pharmacology in the pediatric population	ADME	Age-related differences in PK are expected to a small extent but not expected to have clinical relevance
	Mechanism of action	SGLTi blocks the SGLT2 protein involved in 90% of glucose reabsorption in proximal renal tubule
	Exposure–response relation	After considering differences in drug exposure, eGFR and plasma glucose, the PK–PD relationship on urinary glucose excretion was shown to be similar between adults and youth with T2D
Clinical response to treatment in the pediatric population	Differences	There are no completed efficacy studies with SGLTi. Differences in clinical response could be expected based on differences in disease progression
	Applicability	Efficacy end points (i.e., HbA1c) are applicable in youth as they are in adults

ADME, absorption, distribution, metabolism, excretion; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; PK–PD, pharmacokinetics–pharmacodynamics; SGLTi, sodium/glucose cotransporter inhibitor; T2D, type 2 diabetes.

provided that adequate adult trials have been completed.²⁹ The prevalence of T2D at ages younger than 10 is low, making studies highly impracticable. The pediatric trial for the purposes of drug development is usually a placebo-controlled study in the "add-on to metformin" use-scenario (i.e., with metformin as background therapy), since typical treatment guidelines call for metformin to be used as first-line therapy in both adults and pediatric patients with T2D, and a common treatment paradigm is to continue metformin while adding a second agent when additional glycemic control is needed. In addition, there is an interest from healthcare professionals in assessing efficacy of new drugs in youth with T2D as potential monotherapy because metformin monotherapy fails in many adolescents during the second year of treatment³⁰ or is not tolerated, and because

insulin is not an optimal choice given the route of delivery, the associated weight gain, and the potential risk for hypoglycemia.

Figure 1 depicts the status of completed and ongoing efficacy studies for glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase 4 inhibitors, and SGLT2i drugs in pediatric patients with T2D. The pediatric dose to be investigated in the efficacy and safety studies has been traditionally defined through a separate dose-finding study.¹ This initial dose-finding study is, in general, a short-term treatment PK–PD study in a relatively small number of patients.

The PK–PD relationship after short-term treatment with SGLT2i drugs in youth with T2D has been shown to be similar to adults with T2D.^{2,31–33} As a result, PK–PD studies are no longer part of more recent pediatric plans for SGLT2i drugs, and the

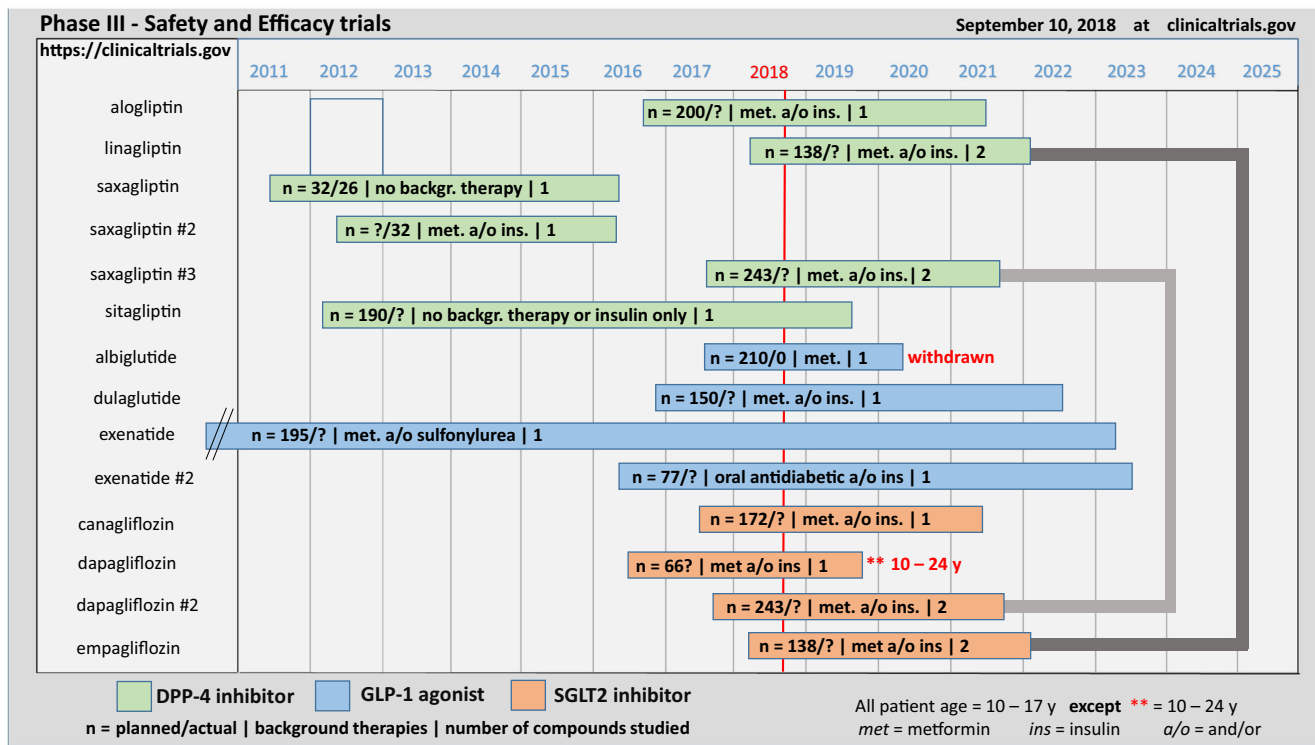


Figure 1 Overview of efficacy studies in youth with T2D. DDP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; SGLT2, sodium/glucose cotransporter 2. [Colour figure can be viewed at wileyonlinelibrary.com]

justification for the dose to be investigated in the efficacy trials is extrapolated by matching blood/plasma concentrations of the drug in youth with adults with T2D.³⁴ However, because of the differences in disease progression and manifestation between these two populations,^{3–6} a similar short-term PK–PD relationship may not necessarily translate into a similar response after long-term treatment, 24 weeks or more.

TOOLS TO INCREASE EFFICIENCY OF PEDIATRIC CLINICAL PROGRAMS

MIDD

Considering obvious similarities between adult and pediatric T2D (i.e., basic pathophysiology of insulin resistance and progressive β -cell dysfunction), Karres *et al.*¹⁶ proposed considerations for the use of extrapolation approaches in pediatric development. However, disease course suggests T2D in the pediatric population may be more aggressive than in adults.³⁵ The use of MIDD^{36–38} can help identify the disease and pharmacological gaps in knowledge between use in adults and pediatric patients leading to uncertainties. MIDD may be beneficial to integrate existing data and prior knowledge in adult and pediatric populations and may provide a starting point for future strategy of T2D pediatric drug development based on prior information. In this context, evidence synthesis based on modeling of relevant data with appropriate assumptions setting, testing, and evaluation should be used. An overview of the quantitative approaches that should be considered is depicted in **Table 3**. The approaches for predicting the drug effect are discussed in this section.

Quantitative systems pharmacology (QSP) models may be one approach to integrate existing knowledge in adult and pediatric

populations because they may be able provide understanding of the system and mechanism of action of the medicinal product under investigation.³⁹ Initially these models could aid in the design and interpretation of dose-finding studies, but if in the future the model assumptions are well understood and validated for context of the intended use, such as replacing studies, they could serve as the basis for pediatric extrapolation. While efforts are made to develop QSP models for adult T2D,⁴⁰ these models are not yet suitable for extrapolation to youth with T2D primarily because of the lack of complementary primary data in youth creating gaps resulting in high uncertainties when using these models. For example, T2D disease progression represented by insulin resistance, plasma glucose, and insulin production is often depicted as static from ages 0 to 20 years, ignoring the pediatric population and the unique time scale and progression it encompasses.⁴¹

Mechanistic disease response models (models with a structure that makes explicit hypotheses about the biological mechanisms that drive dynamics) developed using existing adult and pediatric data could be of value to address project-specific questions. These models have a lower degree of complexity than QSP models as they only consider parameters identified/assumed as key and fit for purpose for the medicinal product under development. Mechanistic disease response models can be developed in a relatively short period of time, though they lack a clinically relevant framework. These models can aid the design and interpretation of data from dose-finding studies. For the hypothetical SGLT2i, PK–PD models could be used to quantify the effect of hyperfiltration as observed in youth with T2D on urinary glucose excretion and plasma glucose.⁴² Also, this model could be extended to allow greater insulin resistance, higher insulin secretion, and more rapid loss of β -cell function to be accounted for. The optimal approach is dependent on the existing data collected in pediatric T2D.

Finally, empirical PK–PD models (models with a structure that does not make explicit hypotheses about the biological mechanisms that drive dynamics) using HbA1c is recommended for the analysis of clinical response to treatment using the data from pivotal efficacy study in youth with T2D. Combining data from pivotal efficacy studies in adults and pediatrics when using the same background therapy could aid identifying and quantifying age-dependent changes and ultimately support dosing recommendations. Additionally, by the time of marketing authorization, it is acknowledged that the data generated in youth with T2D may not fully address all uncertainties related to growth and maturation or long-term use. Therefore early planning to mitigate residual uncertainties in the postauthorization setting should be considered and updated in response to the results of the studies conducted.

As more studies are completed in youth with T2D, considering that the knowledge is adequately captured and accumulates over time, approaches such as QSP models, as well as model-based meta-analyses, could help to support assumptions or make predictions for treatment effects in a pediatric target population, thus providing a rationale for future T2D pediatric drug development. The PK profile at the target age range can be

Table 3 Overview of quantitative approach to assess and utilize evidence

Disease manifestation and progression	<ul style="list-style-type: none"> • Model-based meta-analysis (MBMA) can integrate prior reported data to quantify dose–response (efficacy) in both populations • Mechanistic and quantitative systems pharmacology (QSP) models can integrate how differences in disease manifestation and progression in youth are expected to impact efficacy • Real-world data and/or historical data from controlled pediatric clinical studies can be used to develop mechanistic models to quantify disease progression in both populations
Pharmacology	<ul style="list-style-type: none"> • PK models and allometric scaling is expected to provide adequate prediction of exposure (expected to be similar to adults) • PK–PD model can quantify the relationship between exposure and markers of response using dose-finding studies (short-term response expected to be similar to adults)
Clinical response to treatment	<ul style="list-style-type: none"> • PK–PD model can quantify the relationship between exposure and HbA1c considering the differences in disease progression (long-term response expected to change when compared with adults due to differences in disease progression)

HbA1c, hemoglobin A1c; PK–PD, pharmacokinetics–pharmacodynamics.

adequately predicted from the PK profile in adults using allometric scaling.^{43,44}

Efficient innovative approaches

Examples of changes in study design to address operational challenges related to the enrollment of pediatric patients include allowance for patients on antidiabetics randomized with or without washout even if a stabilization period is required, or allowance for enrolling non-treatment-naïve patients without a washout period to reestablish baseline HbA1c. These measures may lead to increased variability and trial failure. An alternative approach to address enrollment challenges that has been proposed is the use of external controlled clinical trial data (e.g., placebo plus background response data from similarly designed pediatric clinical trials) to the concurrent control or treated patients. Certain study entry criteria could be applied to exclude noncomparable patients, e.g., based on age, BMI, body weight, HbA1c, concomitant antidiabetic treatments, and/or history of diabetic ketoacidosis. Comparisons can also be made after stratifying patients on important covariates. The information obtained from the pooled data can then be synthesized and used to augment the concurrent control or as a prior.

The use of pooled placebo data from controlled clinical trials could provide the closest cohort to the population being studied in the trial. For example, it may give some assurance that populations between external control and concurrent control are comparable in terms of elements important to control bias, including social economic status, and comorbidities depending on the study population of the trial from which the control data are obtained, including when and where the trial was conducted. It is important to note that sufficient pooled data from modern youth onset pediatric trials may not be readily available immediately (industry-sponsored phase III trials that are either just completed (only ELLIPSE - Evaluation of Liraglutide in Pediatrics with Diabetes) or planned for completion in 2019, can be narrowed to four studies (Table 4)). Including ELLIPSE, the total estimated number of subjects assigned to placebo across these studies is 287 if completed as planned in 2019. Expanding out to 2020, there is 1 additional study including about 36 subjects on placebo. This study is still registered as "recruiting"; hence the timelines are likely much more uncertain.

External controls should be carefully selected to minimize bias when comparing outcomes with patients receiving active treatment in the open-label study. The use of more than one external control may be advisable, providing that the analytic plan specifies conservatively how each will be used in drawing inferences. The success of leveraging external data requires that concerns about data availability, quality, and completeness be adequately addressed. However, all the approaches above have the potential to decrease the size of the control arm (and potentially the treatment arm) in a randomized study and to increase study power relative to traditional randomized trials.^{45,46} Ultimately, these data sources and approaches should be used in a thoughtful, fit-for-purpose manner taking into account the specific investigational treatment of interest.

A simulation study was conducted utilizing the designs described above to provide a benchmark for sample sizes that provides the

opportunity to collect robust data to determine the efficacy of the investigational treatment. Table 5 shows the results of power for the three methods as a function of the observed effect, standard deviation in the clinical trial, and the size of the external pooled placebo sample used. The three methods are described in the table. Here, the trial design is to randomize asymmetrically to placebo and investigational treatment, both on background metformin, in a 1:3 ratio with total sample size of 100 (placebo $N = 25$, investigational treatment = 75). The response rate for a 6-month change from baseline of HbA1c for the new investigational treatment is assumed to be -0.30 to -0.5 , while the 6-month change from baseline of HbA1c for placebo is assumed to be 0 with a standard deviation of 1.6. These response rates are translated from what was observed in the Glucovance (glyburide plus metformin) trial, whose two treatment arms resemble the typical background metformin commonly used in pediatric studies. The treatment response for metformin in this trial is -0.48 and the glyburide-metformin arm is about -0.8 . This approach relies on the assumption that the patient characteristics/demographics of the older trials are comparable to contemporary youth-onset diabetes. With higher than usual standard deviation in youth T2D, a new investigational treatment must have a sizeable effect size; otherwise, the only way that a trial can be adequately powered is through the use of these pooled placebo data used to augment the concurrent control or as a prior.

Such innovative analyses may also help to contextualize any benefit demonstrated using a traditional frequentist analysis.

Strategic collaborative approaches

Integration of existing knowledge. Historically, clinical trial data have been collected in diverse data formats in independent studies, not addressing gaps in knowledge related to pathophysiology and differences between youth and adults. This has led to difficulties deriving expectations for drug effects of compounds in youth with T2D by means of quantitative synthesis, (mechanistic) disease response models, or QSP approaches. The strength of existing knowledge is highly based on expert judgment or consensus documents, and the weight that can be attributed to it requires a combination of actual data and value judgments. In the context of an MIDD, it is also clear that individual sponsors compile their knowledge from historical data independent of each other and, hence, there is no consensus on what represents a baseline prior from which the various models are constructed. Through collaborative approaches among stakeholders, from academic research, pharmaceutical companies, regulatory drug agencies, policy makers, and patient/parent advocates, existing knowledge from historical data could be integrated in order to foster the development of predictive models for extrapolation of efficacy data from adults to children, as well as the application of innovative analytics (i.e., by pooling of placebo controls from completed or ongoing trials).

Multicomponent/multisponsor trials. To achieve a faster pace and efficiency in pediatric drug development, the concept of multicomponent and/or multisponsor trials has been proposed

Table 4 Industry-sponsored efficacy studies in youth with T2D completed or expected to be completed between May 2018 and April 2020 (accessed May 13, 2019)

NCT number	Title	Acronym	Status	Enrollment	Estimated placebo patients	Interventions	Sponsor/ collaborators	Phases	Start date	Primary completion date	Completion date
NCT01541215	Efficacy and Safety of Liraglutide in Combination With Metformin Compared to Metformin Alone, in Children and Adolescents With Type 2 Diabetes	Ellipse	Completed	135	68	Drug: liraglutide Drug: placebo Drug: metformin	Novo Nordisk A/S	Phase III	November 13, 2012	November 15, 2017	May 23, 2018
NCT01760447	A Study of the Safety and Efficacy of MK-0431A XR in Pediatric Participants With Type 2 Diabetes Mellitus (MK-0431A-289)		Active, not recruiting	110	55	Drug: Sitagliptin + Metformin XR FDC Drug: Placebo to Sitagliptin + Metformin XR Drug: Metformin XR Drug: Placebo to metformin XR Drug: Insulin glargine Biological: Background insulin	Merck Sharp & Dohme Corp.	Phase III	February 17, 2013	September 13, 2019	September 13, 2019
NCT01472367	A Study of the Safety and Efficacy of MK-0431A in Pediatric Participants With Type 2 Diabetes Mellitus (MK-0431A-170)		Active, not recruiting	140	70	Drug: Metformin Drug: Sitagliptin + Metformin FDC Drug: Placebo to Metformin Drug: Placebo to Sitagliptin + Metformin FDC Biological: Insulin glargine	Merck Sharp & Dohme Corp.	Phase III	December 7, 2011	September 25, 2019	September 25, 2019
NCT01485614	Study to Assess Safety & Efficacy of Sitagliptin as Initial Oral Therapy for Treatment of Type 2 Diabetes Mellitus in Pediatric Participants (MK-0431-083)		Active, not recruiting	190	95	Drug: Sitagliptin Drug: Metformin Drug: Placebo to sitagliptin Drug: Placebo to metformin Drug: Glycemic Rescue 1 Biological: Glycemic Rescue 2	Merck Sharp & Dohme Corp.	Phase III	February 10, 2012	October 10, 2019	October 10, 2019
NCT02725593	Study to Evaluate Safety and Efficacy of Dapagliflozin in Patients With Type 2 Diabetes Mellitus Aged 10-24 Years		Recruiting	72	36	Drug: Dapagliflozin Drug: Dapagliflozin placebo	AstraZeneca Parexel Q2 Solutions PRA Health Sciences Covance Laboratories	Phase III	June 22, 2016	April 24, 2020	April 24, 2020

T2D, type 2 diabetes.

Table 5 Simulation data for proposed solutions

Pooled placebo sample size (matched)		Proposed clinical trial in youth ^a		Power of the proposed clinical trial		
		Investigational treatment 6-month CFB HbA1C		Frequentist ^b	Bayesian augmented design ^c	Average treatment effect for the treated method (matched controls) ^d
Size	Standard deviation	Mean	Standard deviation			
460	1.6	-0.3	1.4	0.16	0.51	0.50
560	1.6	-0.4	1.4	0.25	0.72	0.76
660	1.6	-0.5	1.4	0.35	0.73	0.77
460	1.8	-0.3	1.4	0.16	0.52	0.50
560	1.8	-0.4	1.4	0.25	0.72	0.77
660	1.8	-0.5	1.4	0.35	0.73	0.77
460	1.6	-0.3	1.6	0.12	0.38	0.36
560	1.6	-0.4	1.6	0.18	0.57	0.60
660	1.6	-0.5	1.6	0.26	0.74	0.80
460	1.8	-0.3	1.6	0.12	0.39	0.36
560	1.8	-0.4	1.6	0.18	0.57	0.62
660	1.8	-0.5	1.6	0.26	0.74	0.80

^a6-month change from baseline (CFB) HbA1C (hemoglobin A1c) for control arm is 0. ^bDoes not incorporate external pooled placebo data; assumptions based on 3:1 randomization and calculated through Nquery using simple t-test. ^cUses the external control data as prior for the parameter for the mean of the concurrent control (Pbo). Bayesian decision criterion is $P(IT_x - Pbo > 0) < 0.025$. ^dMatched patients from external control are combined with the concurrent control. Testing is using simple t-test between independent groups in R.

as a solution.⁴⁷ In rare disease therapeutics development, the FDA and the EMA have issued draft guidance designed to help pharmaceutical companies test multiple drug candidates in clinical trials (e.g., Gaucher disease).^{48,49} Multicomponent/multisponsor studies could help to address rare and/or competitive research environments, reducing recruitment challenges while identifying candidate drugs more efficiently in phase I to move into pediatric dose-finding studies. This type of collaborative trial design could also benefit patients by helping to minimize the number of study participants through utilization of a single control group for multiple potential treatments as a comparator. It is envisaged that early constructive dialogue between essential stakeholders could lead to alignment on what constitutes the appropriate biomarkers and/or clinical end points for study and establish data-driven decisions at prespecified timepoints on which a compound (or set of compounds) is appropriate to be moved into the next phase of development. Therefore, these types of trials must carefully consider design methodologies that can effectively address the varied timetable at which new investigational drugs move from discovery into development, impacting the availability of early data needed to inform data-driven prioritization decisions. The vision is that multicomponent and/or multisponsor trials could be a more efficient means to bring candidate compounds forward, all the while focusing resources (patient, study personnel, regulatory personnel, and financial) on the most likely compound to deliver meaningful benefit to patients.

Recently, two sponsors have designed and are recruiting multicomponent trials as single company solutions to enhance the efficiency of their pediatric product development (DINAMO, Diabetes Study of Linagliptin and Empagliflozin in Children

and Adolescents with T2DM⁵⁰ and Study to Evaluate Safety and Efficacy of Dapagliflozin and Saxagliptin⁵¹; **Figure 1**). In both trials each of the two companies has utilized randomized, placebo-controlled, parallel group designs with each active treatment planned to be evaluated in relation to placebo. These examples highlight that multicomponent trials are being utilized by drug developers as innovative solutions to facilitate data generation in pediatric populations. To date, however, no multisponsor trials in pediatric patients with T2D have been agreed or initiated.

An example of how multicompany trials have been done is the National Cancer Institute’s I-SPY 2 adaptive phase II trial platform in adults with cancer.⁵² Developed originally for breast cancer, this model assessing novel drugs is also being applied to colorectal cancer, melanoma, lymphoma, human immunodeficiency virus, and other diseases. It tests the effects of novel cancer drugs against standard therapy on biomarkers that are then correlated with the end point. In this model, a well-performing drug progresses into its own small phase III trial when it has demonstrated a high Bayesian predictive probability of being more effective than standard therapy, which the company then conducts on its own while a new drug enters the joint phase II trial. To participate in I-SPY 2, companies sign a unified intellectual property agreement that was developed by the Foundation of the National Institutes of Health, which also holds the investigational new drug and interacts with the FDA.

A consortia-based approach to designing multicomponent and/or multicompany trials could be an effective means to reaching a consensus on evaluation of therapies, the appropriateness of trial end points, biomarkers, and trial designs, for pediatric diseases. Consortia that are attempting to tackle broad-based solutions to

facilitate pediatric product development should not only include scientific experts in academia, government, and industry but also regulatory, legal, and policy experts to address other parallel issues, including but not limited to prioritization, data sharing, regulatory filing, and decision making.

CONCLUSIONS AND GENERAL RECOMMENDATIONS

Differences in disease progression and manifestation of youth with T2D challenge the ability to leverage data in adults with T2D as part of a pediatric extrapolation approach to drug development. Hence, there is a role for innovative approaches to data generation and analytics to be considered to enhance the efficiency of pediatric drug development programs without compromising the scientific validity of study results. The use of MIDD, efficient innovative analytics, and strategic collaborative trials offers pathways forward to address the needs of youth with T2D.

To make optimal use of the MIDD concept, existing knowledge should be integrated in the development of predictive models through strategic collaborative approaches including stakeholders from academic research, pharmaceutical companies, regulatory drug agencies, and policy makers as well as patient/parent advocates. In addition, the use of pooled placebo from completed or ongoing controlled clinical trials to reduce the allocation to placebo and augment the information of concurrent placebo can potentially make trials more efficient. Moreover, alternative designs should be considered, including multicomponent/multicompany trials having the potential to significantly reduce the number of pediatric T2D patients to be recruited without compromising the interpretability of the study. Finally, for sponsors to use resources most efficiently, global regulatory consensus on the approach is needed.

To facilitate the acceptance of these approaches for new investigational drugs in pediatric drug development in general and in T2D specifically, the authors propose:

- Consensus building on key data and prior knowledge as a basis for evidence synthesis to derive expectations for drug effects in youth with T2D. Creation of a multistakeholder platform to foster collaborative solutions facilitating design and conduct of research in youth with T2D to improve ethical, scientific, and clinical quality of pediatric studies.
 - We propose that the EMA and the FDA, along with other regulatory regions, hold a joint multistakeholder workshop or a series of workshops to align on an effective and efficient development pathway for the T2D therapies that will be used in youth. The focus should include identifying solutions for those investigational therapies currently under evaluation and for the development of new classes of drugs.
- Strategic collaboration facilitating reuse and integration of (clinical) data with the aim of getting a better understanding of the efficacy (and safety) of antidiabetic drugs in youth with T2D and for facilitating the application of Bayesian augmented designs.
 - In the current competitive innovation environment for investigational therapies, collaborative use of clinical data and

multisponsor trials may not be feasible as an option in the premarket setting. We propose that companies agree on a consortium structure that creates a shared central database for consistent capture of natural history data to foster the application of MIDD and efficient innovative approaches in clinical development programs of investigational therapies in youth with T2D.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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AUTHOR CONTRIBUTIONS

All authors have equally contributed to the preparation of this manuscript.

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