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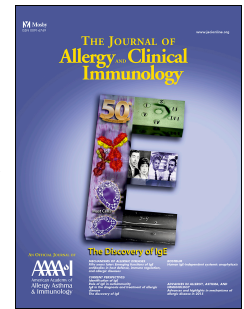
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Effect of Grass Sublingual Tablet Immunotherapy is Similar in Children and Adults: A Bayesian Approach To Design Pediatric Sublingual Immunotherapy Trials

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Conflict of Interest

D. Skoner has served on advisory boards for Meda/Mylan and Genentech, and served as a speaker for Merck & Co., Inc., Kenilworth, NJ, USA, Meda/Mylan, Stallergenes/Greer, and Boston Scientific. J. Ibrahim has nothing to disclose. R.F. Lockey has nothing to disclose. M. Blaiss has served as a consultant for ALK and Stallergenes/Greer. A. Bufe is an associate of

Protectimmun GmbH but has no other commercial relationship to this company. J.S. Andersen was an employee of ALK, Hørsholm, Denmark at the time of the work. G.W. Canonica has served as a consultant and lecturer for ALK, Stallergenes/Greer, and Hal Allergy. A. Kaur and Q. Li are employees of Merck & Co., Inc., Kenilworth, NJ, USA. H. Nolte was an employee of Merck & Co., Inc., Kenilworth, NJ, USA at the time of the work and is now an employee of ALK, Hørsholm, Denmark.

Abstract

Background: Large sample sizes are needed for sublingual immunotherapy (SLIT) trials due to inherent data variability secondary to inconsistent allergen exposure. Obtaining large sample sizes for pediatric SLIT trials is challenging, but a Bayesian approach using prior adult data can reduce the necessary sample size.

Objective: To describe how a Bayesian framework utilizing prior information from adult trials can be used to improve pediatric SLIT clinical development.

Methods: Data were compiled using a frequentist approach (conventional clinical trial approach independent of prior data) from trials conducted during the clinical development of timothy grass SLIT-tablet.

Results: The treatment effect of timothy grass SLIT-tablet was considered similar between pediatric (N=795) and adult (N=2299) data pools, with relative total combined symptom plus medication score improvement (95% CI) vs placebo of 21% (11.0, 30.4) and 20% (14.6, 24.4), respectively. *Phleum pratense*-specific IgG₄ and IgE blocking factor increased from baseline in both children and adults treated with timothy grass SLIT-tablet. Given the reasonable assumption in similarity of treatment response between adults and children, a Bayesian approach is described to demonstrate rigorous efficacy criterion for pediatric trials incorporating information from prior adult trials, and thereby reduce the sample size.

Conclusions: Data support the similarity of efficacy and immunologic changes between children and adults treated with SLIT for allergic rhinoconjunctivitis. Therefore, it is appropriate to utilize data from adult trials to design feasible trials in children, which may reduce unsafe off-label use by promoting more quickly proper labeling of approved products.

Key Messages

- Data from grass SLIT-tablet trials provide evidence that the efficacy and immunologic effect of SLIT are similar between children and adults.
- A Bayesian approach that allows utilizing adult data provides a reasonable framework when designing future pediatric SLIT trials that are feasible to conduct with smaller sample sizes compared to stand-alone trials.
- A hybrid approach of frequentist (using current data) and Bayesian framework (using prior and current data) in study design and data analysis can provide a reasonable path forward to evaluate efficacy and safety of SLIT products in the pediatric population.

Capsule Summary

SLIT effects are similar between children and adults. Analytical approaches that allow borrowing information from adult data are appropriate and will make future pediatric SLIT trials more feasible and therefore, quicker to complete, possibly reducing unsafe off-label use of non-approved SLIT formulations.

Key words: sublingual immunotherapy; children; adults; efficacy; IgG4; Bayesian framework; frequentist; trial design

Abbreviations

AIT: allergy immunotherapy
AR/C: Allergic rhinitis with or without conjunctivitis
FDA: US Food and Drug Administration
SCIT: subcutaneous immunotherapy
SLIT: sublingual immunotherapy
TCS: Total combined score

Introduction

Pediatric trials of new allergy immunotherapy (AIT) treatments are typically conducted subsequent to establishing efficacy and safety in the adult population. There are inherent challenges in conducting large pediatric trials in a reasonable timeframe in situations when efficacy evaluation in pediatric subjects requires the same strict bar as in adult trials. The solution for a feasible pediatric development may lie in a hybrid approach of frequentist (the standard statistical approach used in clinical trials which does not require any prior information to draw conclusions) and Bayesian framework (using prior and current data) in the study design and data analysis after the similarity of effect between adults and children has been reasonably established.¹

Unlike many chronic disorders, allergic rhinitis with or without conjunctivitis (AR/C) affects both children and adults. There is a large body of evidence that demonstrates the efficacy and safety of subcutaneous (SCIT) and sublingual immunotherapy (SLIT) for the treatment of AR/C in adults.²⁻⁴ SLIT may be a particularly attractive treatment option for AR/C in children because it eliminates the need for injections, which children may fear, and it has the advantage of home administration. In the US, grass SLIT-tablets are the only SLIT products currently

approved for children,^{5, 6} and an increasing number of physicians administer SLIT using aqueous extracts approved for subcutaneous AIT despite the lack of documented efficacy and safety data for off-label use.^{7, 8} Thus, there is a need for more pediatric trials for SLIT products.

The US Food and Drug Administration (FDA) criteria to demonstrate efficacy of AIT is based on patient reported outcomes such as symptoms and medication use. The endpoint must show at least a 15% difference versus placebo with a 95% CI lower limit of at least 10% for the primary efficacy outcome.⁹ Several trials show that a sample size of over 1000 subjects may be required¹⁰⁻¹² because AIT field trials are complicated by uncontrollable and variable environmental allergen exposure where patient reported outcome parameters inherently demonstrate relatively large variability.¹³ There is a lower incidence of inhalant allergy in children, making accrual slower (years and multiple seasons) or infeasible and obtaining such a large sample size is more challenging for pediatric than adult clinical trials. It may be impractical to achieve adequate power in the pediatric population and thus, in this case, the only evidence for robust treatment efficacy can be derived from adult AIT trials.

It is natural to consider borrowing information from adult AIT trials since AR/C pathophysiology is similar in children and adults, AIT is dosed similarly in children and adults, and the mechanism of action of AIT is the same.⁴ Bayesian methodology can be applied to improve the power of clinical trials, thereby reducing the sample size needed to adequately demonstrate efficacy. The concept of Bayesian methodology borrows strength from historical information, such as that obtained from adult trials, and incorporates the information to other related populations, in this case, children.¹

Use of Bayesian methodology to leverage information from prior studies is considered for FDA approval of medical devices and is supported by the European Medicines Agency but is

not typically used in late-stage development of pediatric programs.^{14, 15} Furthermore, the FDA Pediatric Research Equity Act guidance suggests that if the course of the disease and effects of the drug are sufficiently similar in adults and pediatric patients, pediatric effectiveness can be reasonably assumed from adequate and well-controlled adult trials.¹⁶ The objective of this analysis is to present evidence suggesting that the efficacy of SLIT treatment is similar in children and adults using a frequentist approach and discuss how a Bayesian approach can be used to improve pediatric SLIT clinical development. In this context, it is important to note that the appropriateness of leveraging efficacy data from adults is independent from extrapolating for the assurance of safety. The safety assessment of SLIT products in children is not discussed in this paper and should be discussed separately based on the regulatory requirements.

Methods

Data sources

The descriptive summary of treatment effect in adults and children was compiled based on historical data from the pediatric and adult phase 3 trials conducted during the clinical development of timothy grass SLIT-tablet (Merck & Co., Inc., Kenilworth, NJ, USA/ALK-Abello, Hørsholm, Denmark). The trials were randomized, double-blind, placebo-controlled trials and are previously described.^{10, 17-21} Key inclusion criteria for all the trials were a clinical history of physician-diagnosed grass-pollen-induced AR/C with or without controlled asthma, a history of medication use to treat AR/C symptoms during the previous pollen season, a positive skin prick test and a serum-specific IgE for *Phleum pratense*. Data from GT-12,¹⁸ P05239¹⁷, and the pediatric (<18 years of age) data from P08067¹⁰ were pooled into a “pediatric” pool, and data from GT-08 (year 1),¹⁹ P05238,²¹ GT-14,²⁰ and the adult data from P08067¹⁰ into an “adult” pool. The efficacy outcome for grass SLIT-tablet was the total combined score (TCS), which is

the sum of the rhinoconjunctivitis daily symptom and daily medication scores. The treatment difference relative to placebo was defined as: $(\text{placebo} - \text{study drug})/\text{placebo} * 100\%$. Grass-specific IgG₄ and IgE blocking factor (which represents competition between IgE and non-IgE antibodies for allergen binding) data from GT-08 (year 1), GT-12, GT-14, P05238, and P05239 also were compiled and descriptive statistics provided for different age groups.

One other marketed SLIT-tablet also is available and data for indirect comparison (meaning data were collected from separate studies) of efficacy between children and adults for 5-grass SLIT-tablet (Stallergenes SA, Antony, France) were obtained from two separately conducted trials previously described.^{22, 23} Key inclusion criteria for the two trials were a clinical history of grass-pollen-induced AR/C for 2 previous seasons, a retrospective rhinoconjunctivitis DSS ≥ 12 based on recall of severe days during the previous pollen season, a positive skin prick test to 5-grass pollen, and a positive serum-specific IgE against *Phleum pratense*. The outcome reported is the rhinoconjunctivitis total symptom score.

Bayesian framework

When appropriate, the use of available adult data can be used to facilitate a “posterior” (updated distribution after new data become available) conclusion about children. Within the Bayesian framework, there are generally two ways of incorporating the historical information (adult trials data) into the new trial (pediatric trial):

1. To treat the historical data as a “prior” in the model, and the new trial data as the “likelihood” of the parameter of interest, thereby jointly deriving the “posterior” information using both “prior” and “likelihood”.
2. To treat both the historical and new trials as independent realizations of the same

underlying distribution of true treatment differences. Thus, the historical trial and the new trial are indirectly linked. This is discussed in more detail in the next section.

For purposes of SLIT studies, the quantity of interest would be the treatment difference relative to placebo. It is assumed that the pooled adult data has true treatment difference (between the study medication and placebo) β_A , the pediatric data has true treatment difference (between the study medication and placebo) β_P , and that β_A and β_P are independent and have the same underlying normal distribution with mean μ and standard deviation ν , with a resulting formula of $\beta_A, \beta_P \sim N(\mu, \nu^2)$. Note that β_A and β_P are usually considered fixed unknown parameters in a frequentist framework but in the hierarchical models, β_A and β_P are considered random variables themselves.

Denote the maximum likelihood estimators of β_A as $\hat{\beta}_A$ with standard error $S_A/\sqrt{n_A}$, where n_A is the sample size per arm for the adult data. Also, $\hat{\beta}_P, S_P$, and n_P are defined similarly for the pediatric data. In cases with multiple adult trials and multiple pediatric trials such as the timothy grass SLIT-tablet program, $\hat{\beta}_A$ and $\hat{\beta}_P$ are assumed to be the estimates from a meta-analysis. Assuming normal distribution of the estimators results in the following hierarchical model:

$$\begin{aligned}\hat{\beta}_A &\sim N(\beta_A, S_A^2/n_A) \\ \hat{\beta}_P &\sim N(\beta_P, S_P^2/n_P) \\ \beta_A, \beta_P &\sim N(\mu, \nu^2)\end{aligned}$$

where μ has a non-informative hyper prior, and the value of ν will be elicited based on the historical information and additional details provided in following subsections.

Based on the hierarchical model, one can get the posterior distribution for $\beta_P \mid \hat{\beta}_A, \hat{\beta}_P$ that will allow evaluation of the associated 95% credible interval.¹ Additional details on the model assumptions are discussed below:

Justification of the model assumptions

The following two pivotal assumptions are made for the hierarchical model:

1. Adult and pediatric data are normally distributed around the true treatment means. For the timothy grass trials, whenever the distribution of data deviated from the normality assumption, the non-parametric analyses were performed and the results were compared with those from the parametric analysis under normality assumption. In these trials, numerically larger treatment effects were observed for the primary efficacy endpoints when using non-parametric analysis as compared to the parametric analysis. For planning purposes, and during the designing stage of each trial, the assumption of underlying normal distribution could be considered conservative in the sense that even if the distributional assumption deviates from normality, the proposed sample size would lean towards a conservative direction. .
2. The true placebo-adjusted treatment effects, β_A and β_P , come from the prior distribution $N(\mu, \nu^2)$.

The normality assumption of the prior distribution is relatively robust for such a hierarchical model. μ is given a non-informative hyper prior and usually the format of a hyper prior is less sensitive. The value of ν is discussed in detail below.

The choice of ν

The ν measures the standard deviation of the two populations and indicates the impact for the prior adult data on the pediatric data. As suggested by Schoenfeld et al,¹ the value of ν can be derived from a previous trial with both adult and pediatric data as follows

$$|\hat{\beta}_A - \hat{\beta}_P|/\sqrt{2}$$

One of the most important aspects in building a Bayesian analysis model is to avoid an over-informative prior probability distribution, where a large-sized historical trial is used to build the prior distribution and totally dominates the current smaller-sized trial. The Bayesian hierarchical model used in this study assumes that subjects are exchangeable within each population (pediatric and adult) but not across populations. This assumption enables adult studies to provide strength to the pediatric study, but not as much as if the subjects in different populations are directly poolable. In this sense, it protects against over-reliance on the adult data. However, there are additional variations of Bayesian methodologies that could be considered for incorporating adult information.

Results

Evidence for similarity of SLIT efficacy in children and adults

Trial P08067 evaluated the efficacy of timothy grass SLIT-tablet in children and adults. The treatment effect with timothy grass SLIT-tablet was consistent between children and adults, with a treatment absolute score difference from placebo for TCS based on medians of -1.32 and -0.90 , respectively, which translates to an improvement versus placebo of 32% and 21%, respectively (**Table 1**).¹⁰ Numeric differences between the two age groups were observed; however, the results reveal a trend toward greater efficacy in children. A similar treatment effect

across the age groups was confirmed when comparing the timothy grass SLIT-tablet pediatric and adult data pools (**Table 2**). Note that the analyses in Tables 1 and 2 are based on the conventional frequentist approach.

Additional support for the similarity in efficacy of SLIT between adults and children is provided by results from 5-grass SLIT-tablet trials. The 5-grass SLIT-tablet groups in the pediatric and adult trials reveal a 31% and 29% reduction in the rhinoconjunctivitis total symptom score, respectively.²⁴

Evidence for similarity of immunologic response to SLIT in children and adults

Phleum pratense-specific IgG₄ increases from baseline in those subjects treated with timothy grass SLIT-tablet, regardless of age in pooled timothy grass SLIT-tablet trials (**Figure 1**). Similarly, the IgE blocking factor reveals increased blockade of the IgE antibody with timothy grass SLIT-tablet treatment, which was slightly higher in children vs adults (**Figure 2**). No statistically significant difference across age groups was found in the placebo-adjusted mean change from baseline for IgG₄ or IgE blocking factor. These results are consistent with the clinical efficacy data and corroborate the assertion that the mechanism of action based on the adaptive immune response is analogous in young children, adolescents, and adults. Note that the analyses in Figures 1 and 2 are based on the conventional frequentist approach.

Example of impact of Bayesian model on pediatric trial design

If using the pediatric study only (frequentist approach), the total randomized subjects needs to be 2920 (1460 per arm) for 85% power (**Table 3**). Using methodology proposed by Schoenfeld et al¹, we estimate the parameter of heterogeneity across adults and paediatrics population ν of about 0.1 and a mean treatment difference from placebo of -1.22 using historical data, with a

target relative treatment improvement of 18% with SLIT vs placebo to demonstrate how the Bayesian model can affect sample size and the power of a pediatric SLIT trial. Using these parameters, the sample size of a pediatric trial could be reduced to 290 subjects per treatment arm with 85% power to meet the FDA criteria of at least a 10% lower bound confidence interval, compared with the adult trial sample size of 910 subjects per treatment arm (set from previously described house dust mite SLIT-tablet studies MT-06 and P001)^{11, 25} used in the Bayesian model (Table 3).

Discussion

There are inherent challenges in conducting large pediatric trials in a reasonable timeframe in situations when the efficacy evaluation requires the same strict bar as adult trials. Depending on the course of disease and the similarity of treatment effect across adults and children, a potential solution for a feasible pediatric development may lie in a hybrid approach of frequentist and Bayesian framework in study design and data analysis.

Overall, the grass SLIT trial data from adults and children reveal similar efficacy and immunologic changes, providing reasonable reassurance that SLIT works in a similar manner in adults and children 5 years and older. This result is supported by a 2010 meta-analysis of SLIT for allergic rhinitis that demonstrates the treatment effect in children is similar to that in adults.²⁶ SLIT is somewhat unique in that the dose of SLIT in children and adults is the same because there is limited systemic absorption of the allergens.²⁷ In AR/C, the disease pathophysiology and the effect of the allergens in children and adults are the same. Allergen acts directly on the immune system through antigen processing cells,²⁸ and the immune system is fully mature shortly after birth, with antibody response fully functional by the age of 2.^{29, 30} Therefore, the

response of the immune system to AIT is comparable from the age of 5 years through adulthood. Furthermore, there is no evidence to suggest that the mechanistic treatment effect obtained within one allergen family (among inhalant allergens) will differ between children and adults. Hence, the AIT guidelines do not draw a distinction between age groups with regard to the value and efficacy of treatment nor do they recommend differing doses for adults versus children.⁴

Three trials would need to be completed before applying the suggested Bayesian framework to a future pediatric trial: one adult trial and one pediatric trial from a 'similar' drug, and one adult trial from the same drug. The first two trials are used to estimate/solicit the similarity between adult and pediatric populations and the third trial is used to plan and analyze the upcoming pediatric trial data. The Bayesian analytical approach proposed utilizes the available adult information for analysis of pediatric SLIT studies in order to demonstrate clinically meaningful effect based on the statistical criteria required by the FDA. When there is also a pediatric study completed with the same drug then that information could also be utilized during planning and analysis purposes.

There are several ways to incorporate historical information in study design and analysis.³¹ Other non-Bayesian approaches also could be considered, although the Bayesian approach is intuitive for SLIT because all Bayesian models have a structure that makes them straightforward to integrate the adult information. The proposed hybrid approach is sufficiently powered to demonstrate treatment difference relative to placebo defined as $((\text{placebo} - \text{study drug})/\text{placebo} * 100\%)$ of greater than 15% and utilizes the prior information from adults to provide sufficient power to demonstrate the lower bound of 95% confidence interval of the treatment difference relative to placebo is at least 10%. When proposing a Bayesian framework various sensitivity analysis should be performed to examine the robustness of the underlying assumptions.

Safety is not discussed in this paper though the proposed study design allows for stand-alone safety assessment in the pediatric trials. However, a smaller sample size could result in less robust safety data. Therefore, additional safety studies (e.g. post-marketing surveillance study) in pediatric patients may be warranted to supplement the adult existing data and provide specific safety data of clinical interest in children such as risk of aspiration, swelling of the oral or laryngeal pharynx, or eosinophilic esophagitis.

In contrast to SLIT, using data from adults for application in children may not be appropriate for many other drugs because of pharmacologic and physiologic differences. Indeed, Janiaud et al,³² examined 89 meta-analyses representing 124 drugs and found that similar treatment effects between children and adults were observed for only 36 of the drugs, whereas 14 drugs actually had a significantly different treatment effect. For the 36 drugs with a similar treatment effect, the authors concluded that extrapolation between children and adults was reasonable. Furthermore, the large variation in dosing, extract quality, and manufacturing processes among SLIT products precludes the use of the proposed Bayesian model across various SLIT products. The model should be applied only when assessing the identical SLIT product in children as was used in the adult trials. Discussions with regulatory authorities will be needed to obtain agreement on the criteria to establish similarity between pediatric and adult populations in order to justify borrowing information from historical data.

Due to the inability to conduct pharmacokinetic studies (due to lack of systemic exposure) or to directly correlate biomarkers to efficacy, it is acknowledged that efficacy evaluation of SLIT in pediatric subjects is necessary to meet FDA Pediatric Research Equity Act requirements. Given the reasonable assumption in similarity of treatment response between adults and children, the statistical success criteria based on the 95% confidence interval for licensure in pediatric

patients should not be the same as that required for the initial licensure of the product in adults.

The example implementation of the Bayesian approach for a pediatric SLIT trial presented herein has the potential to decrease the necessary sample size substantially depending on the underlying assumption of variation between the adult study and the pediatric study treatment effects. Therefore, the use of adult SLIT data for pediatric drug development may benefit children as pediatric SLIT trials become more feasible and more quickly completed. Industry may be encouraged to focus on pediatric development of SLIT products as the implementation of using adult data in pediatric trials increases the efficiency of pediatric drug development.³³ Subsequently, availability of approved SLIT products will likely reduce unsafe off-label use of SCIT products for SLIT administration.

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Figure Legends

Figure 1. Summary by age of mean change from baseline in log₁₀ IgG₄ at the end-of-season in pooled timothy grass SLIT-tablet trials. n = Number of subjects with IgG₄ at the end of the season. SLIT=sublingual immunotherapy.

Figure 2. Summary by age of mean change from baseline in IgE blocking factor at the end-of-season in pooled timothy grass SLIT-tablet trials. n = Number of subjects with IgE blocking factor at the end of the season. SLIT=sublingual immunotherapy.

Table 1. TCS for children and adults in trial P08067 of grass SLIT-tablet. Adapted with permission from Maloney et al.¹⁰

Endpoint	Grass SLIT-		Treatment Difference		Improvement vs Placebo†
	Tablet	Placebo	Estimate (95% CI)	P-value	Estimate
Children	N=123	N=127			
Median TCS [‡]	2.77	4.09	-1.32 (-1.9, -0.1)*	0.020	32%
Mean TCS	3.91	5.12	-1.21 (-2.2, -0.2)		24%
Adults	N=506	N=545			
Median TCS [‡]	3.33	4.24	-0.90 (-1.1, -0.3)*	<0.001	21%
Mean TCS	4.29	5.12	-0.84 (-1.4, -0.3)		16%

SLIT=sublingual immunotherapy; TCS=total combined score (defined as sum of rhinoconjunctivitis daily symptom score and rhinoconjunctivitis daily medication score).

*95% confidence intervals were based on the Hodge-Lehmann estimate. P-values were calculated using the Wilcoxon Rank Sum Test.

†Calculated as (placebo – grass SLIT-tablet)/placebo X 100%.

‡Median from the non-parametric model was the prespecified primary analysis.

Table 2. TCS for children and adults from pooled grass SLIT-tablet trial data.

Endpoint	Grass SLIT-		Improvement vs		
	Tablet	Placebo	Treatment Difference*		Placebo†
	Mean	Mean	Estimate (95% CI)	P-value	Estimate (95% CI)
Children	N=389	N=406			
TCS	4.63	5.87	-1.24 (-1.86, -0.62)	<0.001	21% (11.0, 30.4)
Adults	N=1,111	N=1,188			
TCS	5.30	6.59	-1.30 (-1.65, -0.94)	<0.001	20% (14.6, 24.4)

SLIT=sublingual immunotherapy; TCS=total combined score (defined as sum of rhinoconjunctivitis daily symptom score and rhinoconjunctivitis daily medication score).

*Calculated using analysis of variance with treatment and study as factors in the model.

†Calculated as (placebo – grass SLIT-tablet)/placebo X 100%. 95% CI were obtained using the bootstrap method.

Table 3. Power and sample size planning of a pediatric sublingual immunotherapy trial using a Bayesian approach.

Historical Mean Treatment Difference ²⁵	Target Treatment Improvement Relative to Placebo	Total Randomized* (Per Arm)	$\nu^{\dagger}$	“Power” [‡]
-1.22	18.1%	580 (290)	0.2	54.6%
			0.1	85.0%
		696 (348)	0.2	59.3%
			0.1	86.3%
		860 (430)	0.2	64.8%
			0.1	88.1%
		1840 (920) [§]	0.2	85.0%
			0.1	95.0%

*Assuming a dropout rate of 14%.

[†]The standard deviation between the adult study and the pediatric study treatment effects.

[‡]The “power” of the test which rejects the null if the lower bound of 95% credible interval of the true treatment difference in the pediatric study is greater than 10% of the placebo effect.

[§]If using the pediatric study only (frequentist approach), the total randomized subjects needs to be 2920 (1460 per arm) for 85% power.

Note 1: the sample size information for combined adult study is set as 910 per arm (studies MT-06 and P001).^{11, 25}

