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Estimating the effect of nintedanib on forced vital capacity in children and adolescents with fibrosing interstitial lung disease using a Bayesian dynamic borrowing approach

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Abstract

Background: The rarity of childhood interstitial lung disease (chILD) makes it challenging to conduct powered trials. In the InPedILD trial, among 39 children and adolescents with fibrosing ILD, there was a numerical benefit of nintedanib versus placebo on change in forced vital capacity (FVC) over 24 weeks (difference in mean change in FVC % predicted of 1.21 [95% confidence interval: −3.40, 5.81]). Nintedanib has shown a consistent effect on FVC across populations of adults with different diagnoses of fibrosing ILD.

Methods: In a Bayesian dynamic borrowing analysis, prespecified before data unblinding, we incorporated data on the effect of nintedanib in adults and the data from the InPedILD trial to estimate the effect of nintedanib on FVC in children and adolescents with fibrosing ILD. The data from adults were represented as a meta-analytic predictive (MAP) prior distribution with mean 1.69 (95% credible interval: 0.49, 3.08). The adult data were weighted according to expert judgment on their relevance to the efficacy of nintedanib in chILD, obtained in a formal elicitation exercise.

Results: Combined data from the MAP prior and InPedILD trial analyzed within the Bayesian framework resulted in a median difference between nintedanib and placebo in change in FVC % predicted at Week 24 of 1.63 (95% credible interval: −0.69, 3.40). The posterior probability for superiority of nintedanib versus placebo was 95.5%, reaching the predefined success criterion of at least 90%.

Florian Voss and Christian Stock contributed equally to this study.

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Conclusion: These findings, together with the safety data from the InPedILD trial, support the use of nintedanib in children and adolescents with fibrosing ILDs.

KEYWORDS
clinical trial, pediatrics, pulmonary fibrosis, pulmonary function tests

1 | INTRODUCTION

Childhood interstitial lung disease (chILD) comprises a group of rare and heterogeneous lung disorders affecting infants, children and adolescents.[1–3] These include ILDs associated with surfactant protein deficiency, exposures, and connective tissue diseases.[4,5] Some cases of chILD develop pulmonary fibrosis. The processes underlying pulmonary fibrosis in both adults and children include tissue damage, release of fibrogenic growth factors, fibroblast proliferation and transformation, excessive deposition of extracellular matrix, and aberrant remodeling of the lung architecture.[6,7] chILD is associated with significant morbidity and mortality.[2,3] However, the rarity of chILD makes it challenging to conduct clinical trials in this patient population.[2] Further, there is limited evidence on the natural history of lung function in children and adolescents with fibrosing ILD.[7–9]

In adults with fibrosing ILDs, decline in forced vital capacity (FVC) is reflective of disease progression and is associated with mortality.[10–13] Placebo-controlled trials have demonstrated that nintedanib, an intracellular inhibitor of tyrosine kinases, has a consistent effect on slowing decline in FVC in adults with fibrosing ILDs of diverse etiology.[14] Based on these data, and the similarities in the biological pathways that lead to pulmonary fibrosis in adults and children,[2,6,7] the effects of nintedanib in 39 children and adolescents with fibrosing ILD were investigated in the placebo-controlled InPedILD trial.[15] The primary objective of the trial was to determine the dosing and safety of nintedanib in this pediatric population. Changes in FVC % predicted over 24 weeks, a secondary endpoint, favored nintedanib, but it was not feasible to power the trial for this endpoint.

When drug development in adults precedes development in children, partial extrapolation of evidence from adults enables the efficiency of pediatric drug development to be improved.[16–22] Bayesian statistical methods have frequently been applied in this context.[23,24] These methods allow external information to be "borrowed" for the estimation of a treatment effect. Essentially, they yield a weighted average of prior (historical) evidence collected in a source population (adults) and new evidence collected in a target population (children). The weight placed on the prior evidence from adults is a key quantity, especially when, as is usually the case, the evidence base from adults is large and would overwhelm the evidence from a pediatric trial. As individuals may hold different beliefs about the applicability of data from adults to children, and thus would assign different weights to them, a sensitivity analysis to assess inferences over a range of weights is desirable and has been recommended by regulatory authorities.[19] This also allows the impact of the data from adults on the combined evidence to be assessed.

In an analysis that was prespecified before unblinding of the InPedILD trial, we used a Bayesian dynamic borrowing approach, with a tipping point analysis, which incorporated data on the effect of nintedanib in adults weighted based on the opinion of experts, to estimate the effect of nintedanib on FVC in children and adolescents with fibrosing ILDs.

2 | MATERIALS AND METHODS

2.1 | InPedILD trial design

The design of the InPedILD trial (ClinicalTrials.gov NCT04093024) has been published and the protocol is publicly available.[15] Briefly, this trial enrolled children or adolescents aged 6–17 years with fibrosing ILD on high-resolution computed tomography, confirmed by central review, and clinically significant disease based on a Fan score ≥3[25] or evidence of clinical progression. The trial consisted of a placebo-controlled double-blind period of 24 weeks followed by a variable period during which all patients received open-label nintedanib. Dosing was based on weight-dependent allometric scaling. The co-primary endpoints were the area under the plasma concentration–time curve at steady state at Week 2 of nintedanib treatment and the proportion of patients with treatment-emergent adverse events at Week 24. The results of these endpoints have been reported.[15] Spirometry was performed using standardized spirometers according to ATS/ERS guidelines.[26] FVC % predicted values were calculated using equations published by the European Respiratory Society Global Lung Function Initiative.[27] The effect of nintedanib on change in FVC % predicted at Week 24 was analyzed using a mixed model for repeated measures (MMRM).[28] Details of the statistical model are provided in Supporting Information: A.

The InPedILD trial was initiated at each site following approval by the respective institutional review board/independent ethics committee and competent authority according to national and international regulations. Written informed consent and assent (where applicable) were obtained before trial entry.

2.2 | Meta-analysis of effect of nintedanib versus placebo in adults with fibrosing ILDs

To assess the heterogeneity of the effect of nintedanib in adults and make an initial assessment of treatment effect, data from the six Phase II or III international placebo-controlled trials from the clinical development programs of nintedanib in adults with fibrosing ILDs that had a treatment period of ≥24 weeks were included in a meta-analysis. These trials were the TOMORROW trial, two INPULSIS trials and a Phase IIIb trial in patients with idiopathic pulmonary fibrosis (IPF), SENSCIS trial in patients with ILD associated with systemic sclerosis and INBUILD trial in patients with progressive fibrosing ILDs other than IPF[29–33] (Supporting Information: Table S1). Fixed effect meta-analysis and random effects meta-analysis (with the DerSimonian-Laird estimator for the between-study heterogeneity) of the absolute effect of nintedanib versus placebo on change from baseline in FVC % predicted at Week 24 were performed. Individual effect estimates were obtained using MMRM. FVC % predicted was selected over FVC in mL given the difference in lung volume between adults and children and the fact that lung volume in children is increased by growth. Estimation of FVC % predicted was based on age, sex, height, and race/ethnicity.[27] The heterogeneity of the effect of nintedanib across populations was assessed using the I^2 statistic, τ^2, and p-value from a Q-test.

2.3 | Bayesian dynamic borrowing framework for partial extrapolation

A Bayesian framework that allows dynamic borrowing from trials in adults was used for partial extrapolation (Figure 1). To represent the evidence on the treatment effect in adults, a meta-analytic predictive (MAP) prior was derived.[34,35] The MAP prior was a mixture of normal distributions that can be interpreted as the distribution of the treatment effect of nintedanib that would be expected in trials performed under similar conditions. This distribution was "robustified" by adding another normally distributed component (with a defined weight) that implied no treatment effect and had a large variance. The robust MAP prior thus became a weighted mixture of an informative component (the MAP prior) and a weakly informative component that implied no treatment effect.[34] The derivation of the robust MAP prior is described in Supporting Information: B. The effect of the weakly informative component is that information is borrowed dynamically, that is, the more that the evidence from adults and children is in conflict, the less information is borrowed.

The weight w defined for the informative component (with a corresponding weight of $[1 - w]$ for the weakly informative component) was predefined before unblinding of the InPedILD trial. The weight was determined in an expert elicitation exercise, involving nine experts in the treatment of adult or pediatric ILD (K. K. B., E. M. D., R. D., E. K. F., M. Gr., T. M. M., N. S., D. W., L. R. Y.), facilitated by C. S., M. Ga., and F. V. The elicitation process followed the Sheffield Elicitation Framework (SHELF).[36] As part of the exercise, the meta-analysis, the MAP prior based on adult data, and potential trial outcomes covering a range of treatment effects and weights were discussed, together with operating characteristics such as power and type I error. Possible weights ranged from 0 to 1, with 0 representing a belief that data from trials in adults with fibrosing ILDs were not

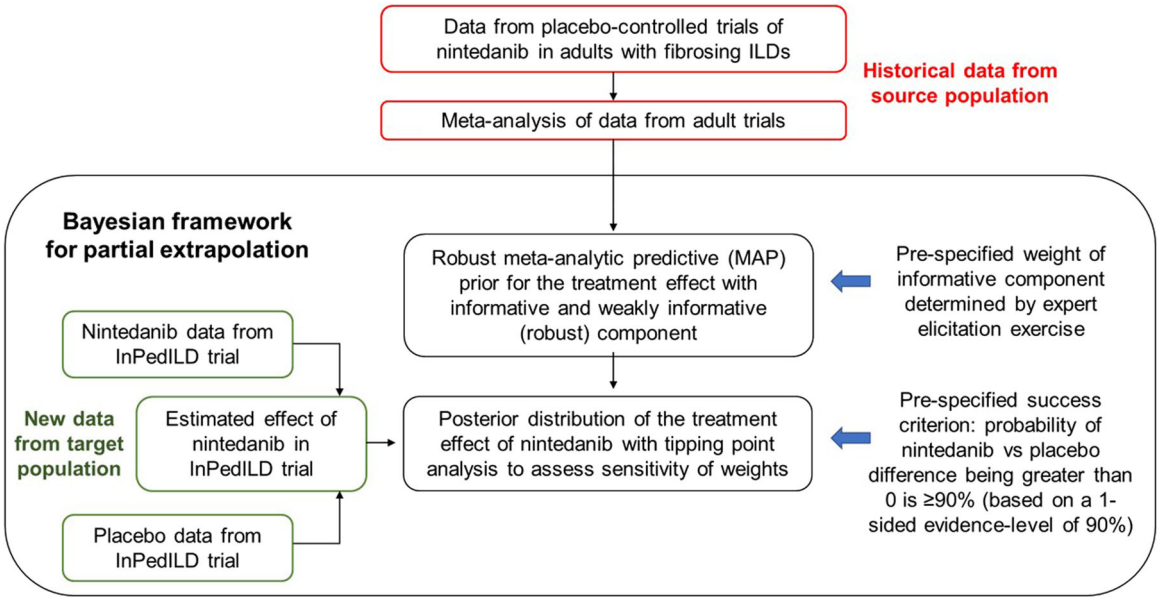


FIGURE 1 Schematic overview of the extrapolation framework. [Color figure can be viewed at wileyonlinelibrary.com]

relevant for making inferences on the effect of nintedanib in the pediatric population, and 1 representing a belief that there would be no difference in the effect of nintedanib between adult and pediatric populations. The beliefs of the experts were approximated by beta distributions. Details of the elicitation task are given in Supporting Information: C.

After completion of the InPedILD trial, the robust MAP prior distribution was updated with the evidence of the effect of nintedanib on FVC % predicted in this trial. This yielded the posterior distribution of the treatment effect of nintedanib in children and adolescents with fibrosing ILD. The posterior distribution thus reflected the estimated treatment effect based on the total available evidence from children, adolescents and adults. A prespecified success criterion for efficacy was defined as a probability of 90% (corresponding to a one-sided significance level of 10%) that the treatment effect was greater than zero for the predefined weight. A tipping point analysis was performed to assess the sensitivity of the results across the range of weights based on four evidence levels: 97.5%, 95%, 90%, and 80% (corresponding to statistical tests with one-sided significance levels of 2.5%, 5%, 10%, and 20%, respectively).

An open-source software package in the R language and environment for statistical computing has been made available to facilitate application of the statistical approaches applied in this article.[37]

3 | RESULTS

3.1 | InPedILD trial results

The InPedILD trial was conducted at 43 sites in 21 countries. Thirty-nine patients (12 aged 6–11 years, 27 aged 12–17 years) were treated (26 with nintedanib, 13 with placebo). The baseline characteristics of the trial population have been published.[15] Briefly, the majority of patients were female (61.5%) and white (79.5%). Mean (SD) age was 12.6 (3.3) years, weight was 42.2 (17.8) kg and FVC was 59.4 (21.9) % predicted. The estimated difference between the nintedanib and placebo groups in the adjusted mean change in FVC % predicted at Week 24 was 1.21 (95% confidence interval [CI]: −3.40, 5.81).[15]

3.2 | Effect of nintedanib on FVC in adults with fibrosing ILDs

In the meta-analysis, the effect of nintedanib versus placebo on the mean change in FVC % predicted at Week 24 in adults with fibrosing ILDs was 1.65 (95% CI: 1.15, 2.14).[15] Treatment effects were consistent across the studies and there was no evidence of heterogeneity in the effect of nintedanib across the trials ($I^2 = 0\%$, $\tau^2 = 0$, $p = .52$). The effect of nintedanib was the same using the fixed effect and random effects models.

3.3 | MAP prior based on adult data (informative component of the prior)

The MAP prior derivation, based on the adult data, yielded a two-component normal mixture with a mean of 1.69 (95% credible interval: 0.49, 3.08) (Supporting Information: Table S2; Figure S1). This prior was used as the informative component for the robust MAP prior.

3.4 | Expert elicitation and predefined robustified MAP prior

Eight of the nine experts chose a similar distribution of the weight with means between approximately 0.5 and 0.7, while one expert chose a mean weight of 0.2 (Figure 2). Combining the distributions, the exercise yielded a mean prior weight on adult data of 0.56 (median 0.58 [Q1, Q3: 0.48, 0.68]). The robust MAP prior with a weight on adult data of 0.56 implied a probability of a treatment effect >0 of 77%.

3.5 | Posterior distribution of the treatment effect

Based on the prespecified prior, combined data from adults and children analyzed within the Bayesian framework resulted in a median difference between nintedanib and placebo in adjusted change in FVC % predicted at Week 24 in children and adolescents of 1.63 (95% credible interval: −0.69, 3.40) (Table 1; Figure 3). The observed treatment effects in children and adolescents and adults did not indicate heterogeneity (prior-data conflict). The probability of the treatment effect of nintedanib being greater than 0 was 95.5%, fulfilling the prespecified 90% evidence level. The weights identified in the tipping point sensitivity analysis for one-sided evidence levels were 0.76 (for 97.5%), 0.52 (for 95%), 0.28 (for 90%), and 0.08 (for 80%) (Figure 4).

4 | DISCUSSION

The rarity of chILD makes it challenging to conduct adequately powered trials in this patient population. In the InPedLD trial, among 39 children and adolescents with fibrosing ILD, there was a positive point estimate for the change in FVC % predicted at Week 24 with nintedanib compared with placebo, surrounded by the uncertainty that would be expected due to the limited sample size.[15] Clinical trials comparing nintedanib with placebo in adults have shown consistent treatment effects on slowing decline in FVC irrespective of the underlying ILD.[14] In the analysis presented here, data on the effect of nintedanib on FVC in adults were incorporated in a Bayesian framework to estimate its effect in children and adolescents with fibrosing ILDs. This approach allows partial extrapolation of the evidence from adults, which has been advocated for ethical reasons and to improve the efficiency of pediatric drug development.[20–22]

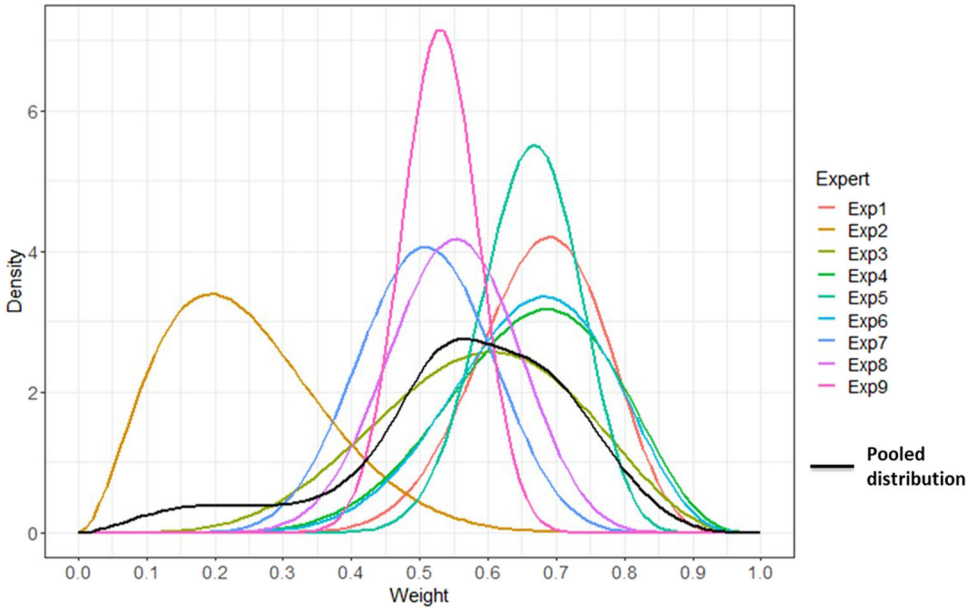


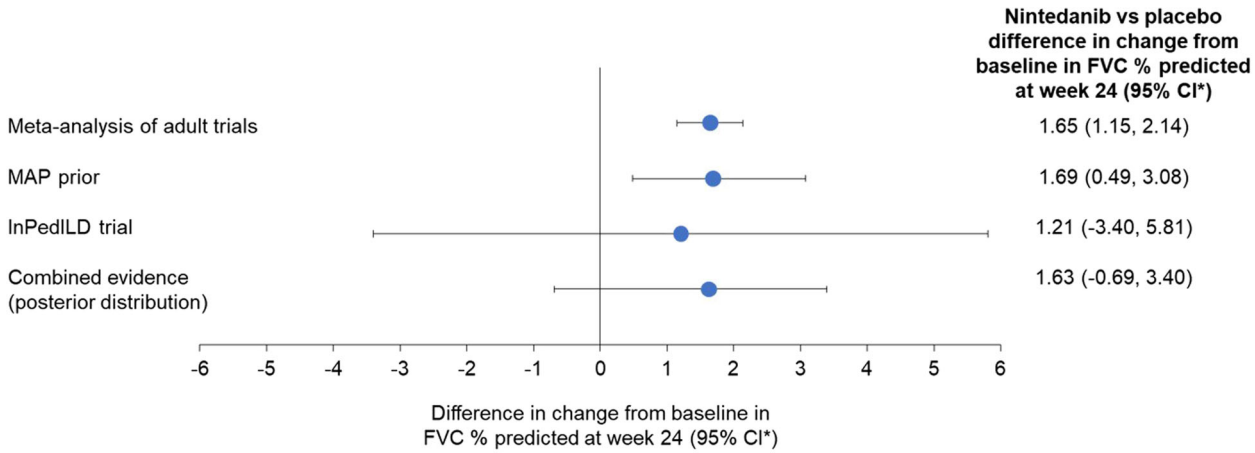
FIGURE 2 Fitted beta distributions and linear pool following expert elicitation. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Posterior distribution of the estimated difference in absolute change from baseline in FVC % predicted at Week 24.

Prior weight on adult data	Nintedanib versus placebo difference in mean change from baseline in FVC % predicted at Week 24 Posterior quantiles									Probability (%) of nintedanib versus placebo difference > 0
	2.5%	5%	10%	20%	Median	80%	90%	95%	97.5%	
0	−3.18	−2.48	−1.67	−0.69	1.17	3.04	4.02	4.82	5.52	70.2
0.1	−2.68	−1.91	−0.99	0.14	1.53	2.42	3.38	4.26	5.03	81.5
0.2	−2.25	−1.40	−0.39	0.72	1.59	2.20	2.93	3.79	4.60	87.2
0.3	−1.84	−0.92	0.11	0.99	1.61	2.12	2.65	3.41	4.20	90.7
0.4	−1.41	−0.45	0.47	1.10	1.62	2.08	2.49	3.13	3.84	93.1
0.5	−0.97	−0.06	0.69	1.16	1.62	2.06	2.41	2.93	3.55	94.8
0.56	**−0.69**	**0.12**	**0.78**	**1.18**	**1.63**	**2.05**	**2.37**	**2.84**	**3.40**	**95.5**
0.6	−0.52	0.22	0.82	1.20	1.63	2.04	2.35	2.79	3.32	96.0
0.7	−0.17	0.42	0.90	1.22	1.63	2.03	2.31	2.70	3.16	97.0
0.8	0.08	0.56	0.95	1.24	1.64	2.03	2.29	2.63	3.03	97.8
0.9	0.26	0.66	0.99	1.25	1.64	2.02	2.27	2.58	2.94	98.4
1	0.39	0.73	1.02	1.26	1.64	2.01	2.25	2.54	2.87	99.0

Note: 0.56 is the prespecified primary weight (the data in this row are the results from the Bayesian framework for this weight).
Abbreviation: FVC, forced vital capacity.

Elicitation of expert opinion to specify informative prior distributions has been recommended to make inferences on the efficacy (and benefit–risk ratio) of an intervention.[36,38] Formal elicitation methods encourage transparent communication on the rationale for believing in the effectiveness of therapy while acknowledging knowledge gaps and uncertainties.[36,38] In this study, elicitation of the weight that should be placed on the informative component based on the adult data in the robustified MAP prior was conducted according to current recommendations to minimize potential biases.[38,39] Based on the average weight placed by the experts on the relevance of the adult data to the pediatric population (0.56), the estimated treatment effect of nintedanib on FVC % predicted over 24 weeks was 1.63%, with a probability for superiority of nintedanib over placebo of 95.5%. The observed treatment effect in the InPedILD trial was 1.21 (95% CI: −3.40, 5.81), which is similar to that observed in adults, supporting the extrapolation. A tipping point analysis demonstrated that even assuming a lower weighting of the adult data, the evidence would suggest efficacy of nintedanib in children and adolescents.



*95% confidence interval for the meta-analysis of the adult trials and the data from the InPedILD trial; 95% credible interval for the MAP prior and combined evidence. Adult trials were the TOMORROW trial, the INPULSIS trials and a Phase IIIb trial in patients with IPF, the SENSCIS trial in patients with SSc-ILD and the INBUILD trial in patients with progressive fibrosing ILDs other than IPF.

FIGURE 3 Nintedanib versus placebo difference in change in forced vital capacity (FVC) % predicted at Week 24 across data sets. [Color figure can be viewed at wileyonlinelibrary.com]

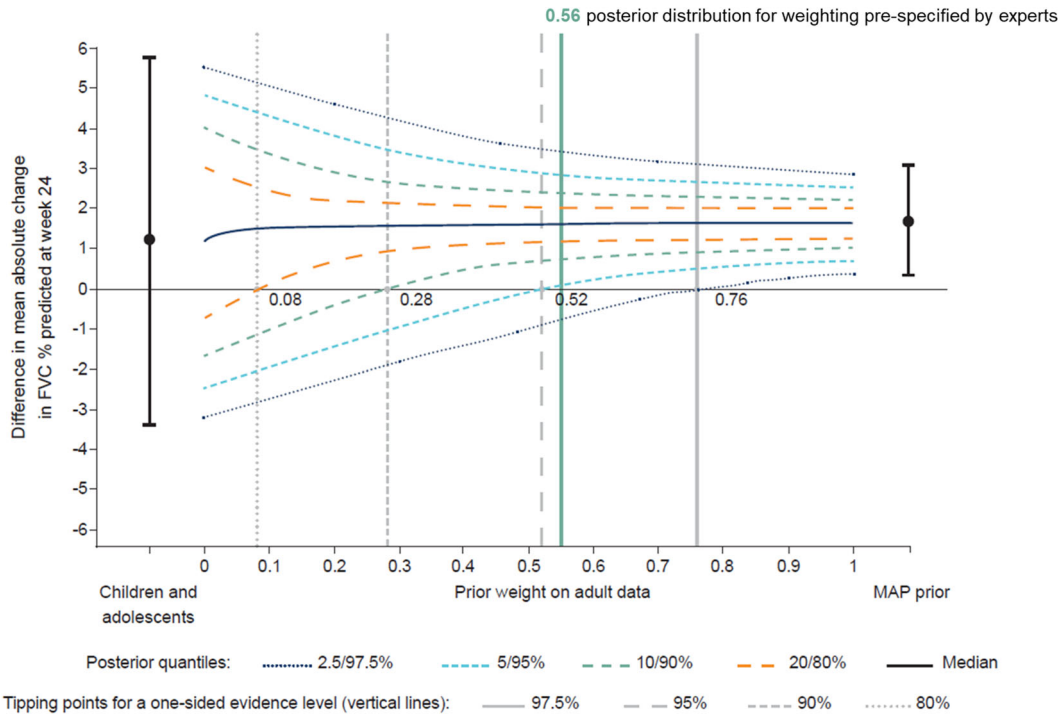


FIGURE 4 Tipping point analysis of change from baseline in forced vital capacity (FVC) % predicted at Week 24. [Color figure can be viewed at wileyonlinelibrary.com]

Bayesian borrowing has been used to estimate the efficacy of medications in various pediatric populations where it is not feasible to conduct adequately powered trials.[40–43] In such cases, it has informed trial design and enabled a reduction in sample size. Our framework for partial extrapolation emphasized transparency and prespecification in all aspects of decision-making, including the use of available data (i.e., the data from adults) for the informative component and the weighting of these data. It combines several features that have been considered desirable in the literature and regulatory guidance on pediatric drug development and may be considered to be a template for trials in similar settings.[18,19,22,23] Our approach achieved a similar power to that which would have been provided by a trial involving 317 pediatric patients (assuming a two-sample *t*-test, a one-sided significance level α of 0.1, 80% power, a standard deviation of 6.51 in each arm, and an allocation ratio of 1:2). The increase in power achieved through use of an informative prior assumes that the adult data are applicable to the

pediatric data. Thus, using this methodology, there is an increased risk of falsely inferring efficacy in situations where there is no treatment effect. At the planning stage of the analysis, the risk of no treatment effect was regarded as unlikely, given the efficacy of nintedanib seen across a broad range of adult populations[14] and the similarities in the biological pathways that lead to pulmonary fibrosis in adults and children.[44,45] We acknowledge the lack of quantitative data on the natural history of ILD in children and adolescents as a limitation of our study.

In conclusion, the present analysis based on a Bayesian borrowing approach, together with the safety findings from the InPedILD trial and the consistent treatment effects observed across the spectrum of ILDs in adult patients, support the extrapolation of the benefits of nintedanib from adults to children and adolescents with fibrosing ILDs. These findings further support the use of nintedanib in children and adolescents aged 6–17 years who have fibrosing ILDs.

AUTHOR CONTRIBUTIONS

Toby M. Maher: Investigation; writing—review & editing. **Kevin K. Brown**: investigation; writing—review & editing. **Steven Cunningham**: Investigation; writing—review & editing. **Emily M. DeBoer**: Investigation; writing—review & editing. **Robin Deterding**: Investigation; writing—review & editing. **Elizabeth K. Fiorino**: Investigation; writing—review & editing. **Matthias Griese**: Investigation; writing—review & editing. **Nicolaus Schwerk**: Investigation; writing—review & editing. **David Warburton**: Investigation; writing—review & editing. **Lisa R. Young**: Investigation; writing—review & editing. **Martina Gahlemann**: Conceptualization; project administration; writing—review & editing. **Florian Voss**: Conceptualization; data curation; project administration; formal analysis; writing—original draft. **Christian Stock**: Conceptualization; data curation; project administration; formal analysis; writing—original draft.

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CONFLICTS OF INTEREST STATEMENT

Toby M. Maher reports consulting fees from AstraZeneca, Bayer, Blade Therapeutics, Boehringer Ingelheim (BI), Bristol Myers Squibb, Galapagos, Galecto, GlaxoSmithKline, IQVIA, Pliant, Respivant, Roche/Genentech, Theravance, Veracyte; and payment for presentations from BI and Roche/Genentech. Kevin K. Brown reports grants from NHLBI; consultancy fees, speaker fees, and/or support for travel for AbbVie, Biogen, Blade Therapeutics, BI, Bristol Myers Squibb, CSL Behring, DevPro Biopharma, Dispersol, Eleven P15, Galapagos, Galecto, Huitai Biomedicine, Humanetics, the Open Source Imaging Consortium (OSIC), Pliant, Redx Pharma, Sanofi, Third Pole, Translate Bio; he reports fees from BI for participation on the Steering Committee of the InPedILD trial; he holds leadership or fiduciary roles with the Fleischner Society and OSIC. Steven Cunningham reports fees paid to his institution by BI for his participation on the Steering Committee of the InPedILD trial. Emily M. DeBoer reports fees from BI for participation on the Steering Committee of the InPedILD trial. Robin Deterding reports consultancy fees, fees for participation on the Steering Committee of the InPedILD trial and support for travel from BI and consultancy fees from Roche. Elizabeth K. Fiorino reports an honorarium and support from Children's Hospital Colorado, and from Simumetrix, LLC for participation in educational events. Matthias Griese reports grants from BI for analysis of the chILD-EU register and fees from BI for membership of the InPedILD Steering Committee, an advisory board, an adjudication board and a web-based series. Nicolaus Schwerk reports consultancy fees from Novartis; payment for lectures from AbbVie, Allergopharma, Chiesi, Infectopharm, Novartis, Pfizer, Sanofi; fees for participation in Data Safety Monitoring Boards or Advisory Boards for BI and Novartis; fees from BI for participation on the Steering Committee of the InPedILD trial; he is a member of the German Society for Pediatric Pneumology, European Respiratory Society, Children's Interstitial Lung Disease Clinical Research Collaboration (chILD-EU), European Cooperation in Science and Technology (COST) network for translational research in children's and adult ILD (ENTeR-chILD) and Secretary of Kinderlungenregister. David Warburton reports a grant re: the RECOVER (COVID-19) initiative from the National Heart, Lung, and Blood Institute (NHLBI) and fees from BI for participation on the Steering Committee of the InPedILD trial. Lisa R. Young reports grants paid to her institution from the National Institutes of Health (NIH) and Orphan Disease Center at the University of Pennsylvania; royalties from UpToDate; consultancy fees and fees for participation on the Steering Committee of the InPedILD trial from BI; consultancy fees from Roche and Sanofi; honoraria from NYU Langone Health. Martina Gahlemann, Florian Voss, and Christian Stock are employees of BI.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. To ensure independent interpretation of clinical study results and enable authors to fulfill their role and obligations under the ICMJE criteria, BI grants all external authors access to relevant clinical study data. In adherence with the BI Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data after publication of the primary manuscript in a peer-reviewed journal, regulatory activities are complete and other criteria are met. Researchers should use https://vivli.org/ to request access to study data and visit https://www.mystudywindow.com/msw/datasharing for further information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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