5-2024

Safety and efficacy of ivacaftor in infants aged 1 to less than 4 months with cystic fibrosis.

Paul McNally

Alvin Singh
Children's Mercy Hospital

Susanna A. McColley

Jane C. Davies

Mark Higgins

See next page for additional authors

Recommended Citation
McNally P, Singh A, McColley SA, et al. Safety and efficacy of ivacaftor in infants aged 1 to less than 4 months with cystic fibrosis. J Cyst Fibros. 2024;23(3):429-435. doi:10.1016/j.jcf.2024.03.012

Journal of Cystic Fibrosis 23 (2024) 429–435

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Original Article

Safety and efficacy of ivacaftor in infants aged 1 to less than 4 months with cystic fibrosis☆

Paul McNally [a], Alvin Singh [b], Susanna A. McColley [c], Jane C. Davies [d], Mark Higgins [e], Meng Liu [e], Jennifer Lu [e], Violeta Rodriguez-Romero [e], Judy L. Shih [e], Margaret Rosenfeld [f,*], on behalf of the VX15-770-124 Study Group

[a] RCSI University of Medicine and Health Sciences and Children's Health Ireland, Dublin, Ireland
[b] Children's Mercy Kansas City, Kansas City, MO, USA
[c] Ann & Robert H. Lurie Children's Hospital of Chicago and Northwestern University Feinberg School of Medicine, Chicago, IL, USA
[d] NHLI, Imperial College London & Royal Brompton Hospital, Part of Guy's & St Thomas' Trust, London, UK
[e] Vertex Pharmaceuticals Incorporated, Boston, MA, USA
[f] Center for Clinical and Translational Research, Seattle Children's Research Institute, and Department of Pediatrics, University of Washington School of Medicine, Seattle, WA, USA

ARTICLE INFO

Keywords:
CFTR potentiator
Ivacaftor
Pharmacokinetics
Infants
Cystic fibrosis transmembrane conductance regulator

ABSTRACT

Background: Ivacaftor (IVA) has been shown to be safe and efficacious in children aged ≥4 months with cystic fibrosis (CF) and CFTR gating variants. We evaluated safety, pharmacokinetics (PK), and efficacy of IVA in a small cohort of infants aged 1 to <4 months with CF.

Methods: In this phase 3, open-label study, infants 1 to <4 months with CF and an IVA-responsive CFTR variant received an initial low dose of IVA based on age and weight. Because IVA is a sensitive CYP3A substrate and CYP3A maturation is uncertain in infants, doses were adjusted at day 15 to better match median adult exposures based on individual PK measurements taken on day 4. Primary endpoints were safety and PK measurements.

Results: Seven infants (residual function CFTR variants [*n*=5]; minimal function CFTR variants [*n*=2]) received ≥1 dose of IVA. Six infants had doses adjusted at day 15 and one infant did not require dose adjustment; subsequent PK analyses showed mean trough concentrations for IVA and metabolites were within range of prior clinical experience. Four infants (57.1%) had adverse events (AEs); no serious AEs were noted. One infant discontinued study drug due to a non-serious AE of elevated alanine aminotransferase >8x the upper limit of normal. Mean sweat chloride concentration decreased (−40.3 mmol/L [SD: 29.2]) through week 24. Improvements in biomarkers of pancreatic function and intestinal inflammation, as well as growth parameters, were observed.

Conclusions: In this small, open-label study, IVA dosing in infants achieved exposures previously shown to be safe and efficacious. Because PK was predictable, a dosing regimen based on age and weight is proposed. IVA was generally safe and well tolerated, and led to improvements in CFTR function, markers of pancreatic function and intestinal inflammation, and growth parameters, supporting use in infants as young as 1 month of age.

1. Introduction

Cystic fibrosis (CF) transmembrane conductance regulator (CFTR) modulators are small-molecule therapeutics that target the underlying cause of CF. Ivacaftor, a CFTR potentiator, improves CFTR function by increasing channel gating activity at the cell surface [1,2]. In clinical trials and real-world studies, ivacaftor has been shown to be safe and efficacious in children as young as 4 months of age with *CFTR* gating pathogenic variants, with early and sustained improvements in lung function, CFTR function, and respiratory symptoms [3–6]. Pancreatic function and growth parameters improved in children treated with ivacaftor [4], strongly supporting the potential for early treatment with ivacaftor to change CF disease progression.

ARRIVAL was a phase 3, open-label study (VX15-770-124;

☆ The full list of investigators can be found in the online supplementary material.

* Corresponding author.
E-mail address: margaret.rosenfeld@seattlechildrens.org (M. Rosenfeld).

https://doi.org/10.1016/j.jcf.2024.03.012
Received 30 November 2023; Received in revised form 8 March 2024; Accepted 25 March 2024
Available online 4 April 2024

NCT02725567) that assessed the safety, pharmacokinetics, pharmacodynamics, and efficacy of ivacaftor in children with CF aged less than 24 months. The study was divided into cohorts based on age; results for children aged 4 to 24 months having been previously reported [4,6]. Here, we describe results from the final cohort of the ARRIVAL study, infants aged 1 to less than 4 months, the youngest patient population to receive CFTR modulator therapy. Because ivacaftor is a sensitive CYP3A substrate and CYP3A maturation is uncertain in this age group, an innovative study design was implemented wherein each infant initially received a low dose of ivacaftor that was subsequently adjusted based on individual pharmacokinetic results to ensure safe dosing.

2. Methods

2.1. Study design and participants

ARRIVAL was a two-part (part A and part B), phase 3, multicenter, open-label study that included sequential decreasing-in-age patient cohorts. Eligible participants in the final cohort were aged 1 to less than 4 months at dosing, had a gestational age of ≥38 weeks, had a confirmed diagnosis of CF, weighed at least 3 kg at the time of treatment initiation (day 1), and had at least one ivacaftor-responsive *CFTR* pathogenic variant. Infants with an *R117H* genotype had to have either the 5T variant or a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis at screening. The study was conducted at four medical centers in the United States and Ireland.

An independent ethics committee or an institutional review board for each site approved the study protocol. Written, informed consent was obtained from each infant's parent or legal guardian. Data were reviewed by an independent data monitoring committee to ensure the safety of the participants in the study. Additional information on study design and inclusion and exclusion criteria can be found in the online supplementary material.

2.2. Procedures

Infants began taking an initial low dose of ivacaftor (5.7 mg every 12 h [q12h] or 11.4 mg q12h based on day 1 age and weight) (Fig. 1). Infants 1 month of age and weighing ≥3 kg received ivacaftor 5.7 mg q12h; infants 2 months of age and weighing ≥3 kg to <5 kg received ivacaftor 5.7 mg q12h; infants 2 months of age and weighing ≥5 kg received ivacaftor 11.4 mg q12h; and infants 3 months of age and weighing ≥5 kg received ivacaftor 11.4 mg q12h. These initial doses were predicted to yield exposures within or below the adult exposure range from pharmacokinetic simulations accounting for uncertainty in CYP3A maturation. Ivacaftor exposures (area under the curve from 0 to 12 h [$AUC_{0\text{-}12h}$] and minimum concentration) were evaluated based on blood samples taken at day 4 and, if appropriate, the dose was adjusted to 5.7 mg, 11.4 mg, 17.1 mg, 22.8 mg, or 25.0 mg q12h on the evening of day 15 to better match median adult ivacaftor exposure. Pharmacokinetic samples were collected before the morning dose on day 4 and between 2 and 4 h and 6 and 8 h after the day 4 morning dose. At day 15, a trough pharmacokinetic sample was collected before the morning dose and the adjusted ivacaftor dose (if needed) was administered q12h starting with the evening dose on day 15. Pharmacokinetic samples were also collected before the morning dose on week 8 and between 2–4 h and 6–8 h after the week 8 morning dose as well as before the morning dose on the week 4, 12, 18, and 24 visits to characterize the longitudinal pharmacokinetic profile for each infant. To account for infants increasing in both age and weight after day 15, ivacaftor doses were increased at scheduled visits over the course of the study according to the approved indication for children ≥4 months of age and weighing ≥5 kg. Participants who completed 24 weeks of ivacaftor treatment in this study were eligible to enroll in an extension study (VX15-770-126). Additional information on dose selection and administration and pharmacokinetic modeling can be found in the online supplementary material (Table S1).

Because this study overlapped with the SARS-CoV-2 pandemic, safety measures were implemented to provide participants with the opportunity to continue the study while minimizing exposure risk, including shipment of study drug to participants' homes, home or local collection of laboratory tests, remote monitoring/source data verification, and remote consenting.

2.3. Outcomes

The primary endpoints were safety, as determined by adverse events, clinical laboratory values (serum chemistry and hematology), standard 12-lead electrocardiograms, vital signs, and ophthalmological examinations, and estimates of pharmacokinetic parameters for ivacaftor and the ivacaftor metabolites M1 and M6. The secondary endpoint was absolute change from baseline in sweat chloride concentration through week 24. Additional endpoints included absolute change from baseline in weight, length, weight-for-length, weight-for-age z-score, length-for-age z-score, and weight-for-length-for-age z-score at week 24, fecal elastase-1, immunoreactive trypsinogen (IRT), fecal calprotectin, qualitative microbiology cultures at week 24, and numbers of pulmonary exacerbations and CF-related hospitalizations.

2.4. Statistical analyses

Sample size was based on the availability of the participant population and pharmacokinetic analysis considerations. All analyses were descriptive. Population pharmacokinetic modeling was conducted to allow comparison to adult exposures. Details on the calculation of number of pulmonary exacerbations or CF-related hospitalizations, as well as the definition of pulmonary exacerbation, can be found in the online supplementary material.

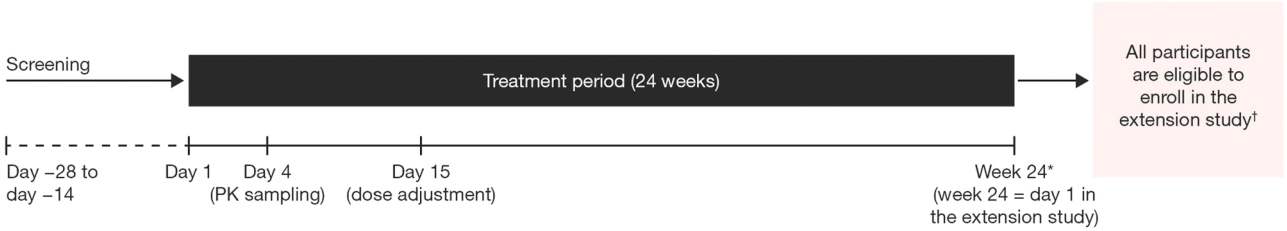


Fig. 1. Study design. Initial dosing (based on day 1 weight and age) was ivacaftor 5.7 mg q12h or 11.4 mg q12h. Dose was adjusted, if appropriate, in the evening on day 15 to either 5.7, 11.4, 17.1, 22.8, or 25 mg q12h based on day 4 pharmacokinetic assessment; no further dose adjustment was made until infants turned 4 months of age and weighed at least 5 kg. *Follow-up ophthalmological examination occurred ~12 weeks after last dose of study drug unless the participant enrolled in the extension study (Study 126) or continued onto commercial drug. †All participants who completed 24 weeks of study drug treatment were eligible to enroll in the open-label treatment arm of the extension study (VX15-770-126). All other participants were eligible to enroll in the observational arm of the extension study. Abbreviation: q12h=every 12 h.

2.5. Role of the funding source

The sponsor of this study was involved in study design, data analysis, and data interpretation.

3. Results

This phase 3 study cohort was conducted between January 27, 2021, and June 28, 2022. Seven infants (mean age at baseline: 1.9 months [range 1 to 3]) were enrolled and received at least one dose of ivacaftor; mean duration of ivacaftor exposure was 22.0 weeks (range: 9 to 25). Two infants had the *G551D/F508del* genotype (minimal function genotype), and the remaining infants had *R117H-9T/F508del, G551D/3197G>A, G551D/R117H-7T, S945L/N1303K*, or *R117C/W1282X* genotypes (residual function genotypes) (Table 1). Mean sweat chloride concentration was 73.8 (standard deviation [SD]: 19.1) mmol/L at baseline, reflecting the preponderance of residual function genotypes. Growth parameters at baseline were within the normal range, but below median of the reference general population [7]. Adherence with study drug was 100% based on the number of sachets taken. Additional baseline demographic and clinical characteristic data can be found in Table S2.

Six of seven infants (85.7%) completed ivacaftor treatment; one infant interrupted treatment on day 63 and discontinued treatment on day 173 due to an adverse event of elevated alanine aminotransferase associated with viral illnesses, described in more detail below (**Fig. S1**). The initial ivacaftor dosing regimen was established based on population pharmacokinetics modeling to ensure exposures were within or below the range of prior experience in older age groups. Based on day 1 age and weight, three infants received an initial ivacaftor dose of 5.7 mg q12h and four infants received an initial dose of 11.4 mg q12h (**Table S3**). As expected, pharmacokinetic analyses conducted on samples taken at day 4 showed ivacaftor exposures on the initial low dose were at the low end of the range of prior clinical experience (Fig. 2). To better match median adult ivacaftor exposures, six of the seven infants had their ivacaftor dose adjusted at day 15; one infant had exposures within the adult range and did not require adjustment. Following dose adjustment, mean trough plasma concentrations of ivacaftor, M1-ivacaftor, and M6-ivacaftor were within the range of prior clinical experience and trough concentrations of all analytes were generally comparable across visits, consistent with the expected steady-state profile of ivacaftor (**Table S4**). Population pharmacokinetic analysis demonstrated that $AUC_{0\text{-}12h}$ exposures for ivacaftor after dose adjustment at day 15 were within the range previously shown to be safe and efficacious in older children and adults (Fig. 2).

Table 1
Demographics and baseline clinical characteristics.

	Participants (*N*=7)
Sex, n (%)	
Male	3 (42.9)
Age at baseline, mean (SD), months	1.9 (0.9)
1 month old at study day 1, n (%)	3 (42.9)
2 months old at study day 1, n (%)	2 (28.6)
3 months old at study day 1, n (%)	2 (28.6)
Weight at baseline/day 1, mean (SD), kg	4.9 (0.9)
Race, n (%)	
White	7 (100.0)
Ethnicity, n (%)	
Not Hispanic or Latino	7 (100.0)
Geographical region, n (%)	
North America	3 (42.9)
Europe	4 (57.1)
CFTR genotype,* n (%)	
F508del/G551D	2 (28.6)
F508del/R117H	1 (14.3)
G551D/3197G>A	1 (14.3)
G551D/R117H	1 (14.3)
N1303K/S945L	1 (14.3)
R117C/W1282X	1 (14.3)
Sweat chloride, mean (SD), mmol/L	73.8 (19.1)
Weight-for-length z-score, mean (SD)	−0.87 (0.66)
Fecal elastase-1, mean (SD), μg/g†	344.8 (197.5)
Pancreatic insufficient (fecal elastase-1 values ≤200 μg/g), n (%)	2 (28.6)

*Two participants had genotypes associated with pancreatic insufficiency (*G551D/F508del*) and 5 participants had residual function genotypes generally associated with pancreatic sufficiency.

† *n*=6. Abbreviations: CFTR=cystic fibrosis transmembrane conductance regulator; SD=standard deviation.

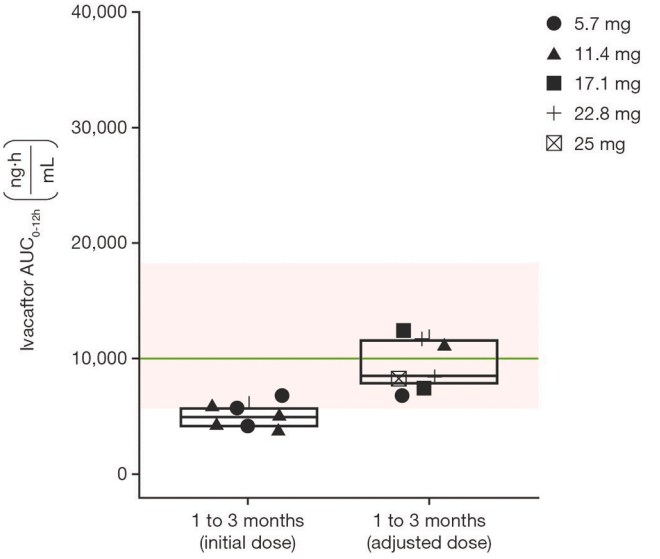


Fig. 2. Ivacaftor individual-predicted exposures after the initial dose and after the individual dose adjustment in infants aged 1 to less than 4 months. Ivacaftor individual-predicted exposures after the initial dose (left) and the individual dose adjustment (right) in infants aged 1 to less than 4 months. All participants received an initial low dose of ivacaftor (5.7 or 11.4 mg q12h) based on their age and weight at day 1. At day 4, each participant's exposure was evaluated and, if appropriate, the dose was adjusted at day 15 to 5.7, 11.4, 17.1, 22.8, or 25 mg q12h to better match the adult median exposure. Boxplots are the statistics of the individual-predicted exposures in participants from given age group, bolded black lines in center of box are medians, boxes are interquartile range, and whiskers are 1.5× the interquartile range. Shapes represent the individual-predicted exposures of participants enrolled and receiving the initial and adjusted doses. Shaded area represents the adult 5th to 95th percentile region of ivacaftor exposures with the median exposure shown as a green line. The legend shows the administered ivacaftor q12h dose in mg. Six of 7 infants had a dose adjustment (increase). $AUC_{0\text{-}12h}$ corresponds to $AUC_{0\text{-}12h}$ at steady-state. Abbreviations: $AUC_{0\text{–}12h}$=area under the curve from 0 to 12 h; q12h=every 12 h.

Overall, four of seven infants (57.1%) had adverse events, which were all mild in severity; none were considered related to ivacaftor (Table 2). Adverse events were generally consistent with common manifestations of CF in this age group, with no adverse events occurring in more than one participant. One infant discontinued ivacaftor due to a non-serious adverse event of elevated alanine aminotransferase. On day 63, the infant interrupted ivacaftor due to elevated alanine aminotransferase levels greater than eight times the upper limit of normal (9.3×); levels fluctuated following study drug interruption. Alanine aminotransferase levels did not achieve a stable return to baseline levels or less than two times the upper limit of normal and on day 173 the study investigator and infant's family decided to discontinue the infant from the study. The event was assessed by the site investigator as unlikely to be related to ivacaftor and was noted to be concurrent with a gastrointestinal illness and other subsequent viral illnesses experienced by the infant. No other infants had alanine aminotransferase or aspartate

Table 2
Summary of adverse events.

Preferred term, n (%)	(*N*=7)
Participants with adverse events*	4 (57.1)
Adverse events by maximum severity	
Mild	4 (57.1)
Moderate	0
Severe	0
Life-threatening	0
Adverse events by strongest relationship	
Not related	3 (42.9)
Unlikely related	1 (14.3)
Possibly related	0
Related	0
Adverse events leading to discontinuation†	1 (14.3)
Adverse events leading to interruption	0
Adverse events	
Bronchiolitis	1 (14.3)
Constipation	1 (14.3)
Contusion	1 (14.3)
Diarrhea	1 (14.3)
Enterovirus test positive	1 (14.3)
Feces discoloured	1 (14.3)
Human rhinovirus test positive	1 (14.3)
Irritability	1 (14.3)
Nasal congestion	1 (14.3)
Rhinorrhea	1 (14.3)
Vomiting	1 (14.3)
Alanine aminotransferase increased	1 (14.3)
Accidental overdose‡	1 (14.3)

*A participant with multiple events within a category (any, system organ class, or preferred term) was counted only once in a category.
† One infant discontinued treatment due to an adverse event of elevated alanine aminotransferase that was considered unlikely related to study drug.
‡ Caregiver inadvertently gave infant 2 sachets for evening dose instead of 1 sachet (25 mg).

aminotransferase concentrations greater than three times the upper limit of normal (**Table S5**). Four infants (57.1%) had increases in alanine aminotransferase or aspartate aminotransferase concentrations <3x the upper limit of normal. There were no treatment-emergent cataracts, lens opacities, or rash events, and no clinically relevant findings in other laboratory, vital signs, or electrocardiogram parameters.

Following initiation of ivacaftor, infants had rapid decreases in sweat chloride concentration that were generally sustained through week 18, the last study visit with sweat chloride data on four or more infants. The mean absolute change from baseline in sweat chloride concentration was −50.6 (SD: 24.2) mmol/L at day 15 (*n*=4), −46.0 (SD: 24.8) mmol/L at week 4 (*n*=5), −42.5 (SD: 22.9) mmol/L at week 8 (*n*=5), −32.9 (SD: 33.8) at week 12 (*n*=5), and −47.8 (SD: 37.0) mmol/L at week 18 (*n*=4). At the week 24 visit, five infants had insufficient sweat chloride sample volumes for assessment and one infant had discontinued before week 24; only one infant had a sweat chloride value reported. Due to the large number of missing samples at week 24, an ad hoc analysis of the average change from baseline in sweat chloride through week 24 was performed using all post-baseline measurements from these five participants. The mean average change in sweat chloride concentration from baseline through week 24 was −40.3 (SD: 29.2) mmol/L (*n*=5) (**Table S6** and Fig. 3).

Improvements in markers of pancreatic function and intestinal inflammation were also observed over the 24-week treatment period. The mean absolute change from baseline at week 24 in fecal elastase-1 concentration was 103.4 (SD: 131.4) μg/g (*n*=5) (**Table S6** and Fig. 3). Only two of the seven infants were pancreatic insufficient at baseline (fecal elastase-1 values ≤200 μg/g). One infant had an increase in fecal elastase concentration to >200 μg/g at the week 18 visit (fecal elastase-1 ≤200 μg/g at all other study visits) and the other infant had fecal elastase-1 concentrations >200 μg/g from day 4 through week 24. Mean IRT decreased (i.e., improved) over the treatment period, with a mean absolute change from baseline at week 24 of −392.5 (SD: 272.6) ng/mL (*n*=4). Mean fecal calprotectin, a marker of intestinal inflammation, also decreased (i.e., improved) with a mean absolute change from baseline at week 24 of −154.00 (SD: 162.57) μg/g (*n*=5).

Growth parameters, which were all normal at baseline, although below the median of the reference population, increased through week 24. Increases in weight-for-age z-score (+1.14 [SD: 0.89]), length-for-age z-score (+1.12 [SD: 0.61]), and weight-for-length z-score (+0.75 [SD: 1.05]) were observed from baseline through week 24 (**Table S6** and **Fig. S2**).

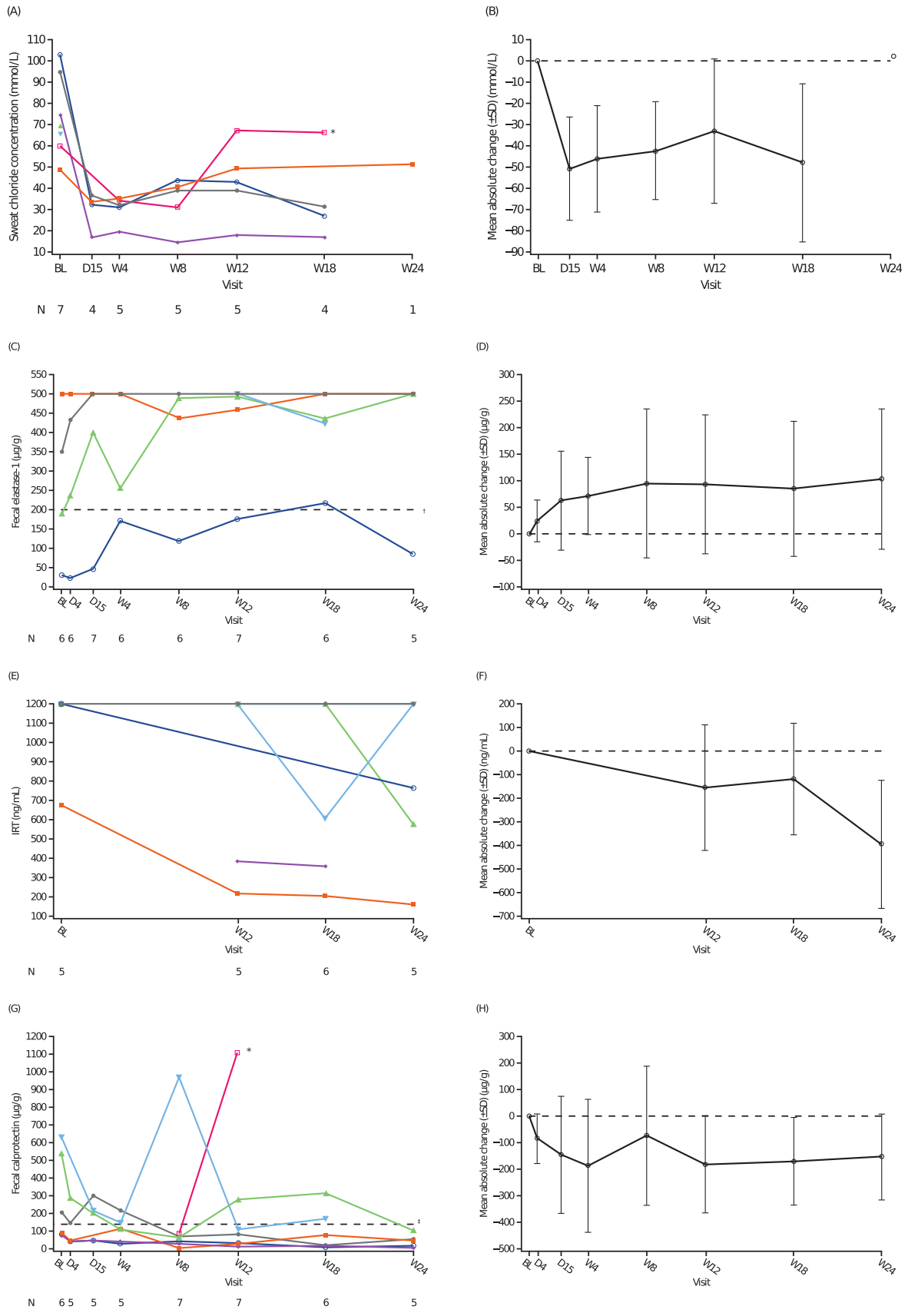
There were no identifiable trends in qualitative microbiology cultures over the 24-week ivacaftor treatment period. No infants had protocol-defined pulmonary exacerbations or CF-related hospitalizations (**Tables S7** and **S8**).

4. Discussion

We assessed the safety, pharmacokinetics, and efficacy of ivacaftor over 24 weeks in a cohort of seven infants aged 1 to <4 months with CF, the youngest patient group treated with ivacaftor or any CFTR modulator to date. To ensure safe dosing given the uncertainty of CYP3A maturation in this age group, we implemented an innovative dose-adjustment protocol in which all infants started treatment at a low dose of ivacaftor and then the dose was individually adjusted at day 15 based on pharmacokinetics at day 4. Following dose adjustment, mean trough plasma concentrations of ivacaftor, M1-ivacaftor, and M6-ivacaftor were all within the range of prior clinical experience in older children, adolescents, and adults [4,6] and ivacaftor $AUC_{0\text{-}12h}$ exposures were near the adult median and within the range previously shown to be safe and efficacious in adults. Since pharmacokinetics were largely predictable in this cohort, we suggest that dosing regimens based on age and weight rather than individualized dosing based on pharmacokinetics can likely be used in this young patient population. These results can help to inform understanding of cytochrome P450 ontogeny showing how CYP3A function matured in infants aged 1 to 4 months, which could be relevant for future treatment options for the youngest infants with CF.

Ivacaftor was generally safe and well tolerated during the 24-week treatment period in this small cohort, with all adverse events being mild in severity and non-serious and generally consistent with common manifestations of CF. One infant discontinued ivacaftor due to an adverse event of elevated alanine aminotransferase/aspartate aminotransferase concentration >8x the upper limit of normal that was not considered by the site investigator to be related to ivacaftor and occurred in the context of recurrent viral illnesses in the infant. The alanine aminotransferase/aspartate aminotransferase concentrations remained elevated after the infant discontinued ivacaftor, which further supports that the adverse event was unlikely related to ivacaftor. Overall, changes in alanine aminotransferase and aspartate aminotransferase levels among all infants in this study were consistent with older age cohorts from the ARRIVAL study [4,6,8].

The mean decrease in sweat chloride concentration from baseline through week 24 observed in the current study (−40.3 mmol/L) was generally comparable to the decreases reported in children aged 4 to less than 6 months (−50.0 mmol/L) and in children aged 6 to less than 12 months (−58.6 mmol/L). It should be noted that, on average, infants in the current study (five of seven of whom were pancreatic sufficient) did have a greater level of CFTR function at baseline, as indicated by lower mean sweat chloride concentration (73.8 mmol/L), compared to children aged 4 to less than 6 months (97.4 mmol/L) and children aged 6 to less than 12 months (101.5 mmol/L) [4,6,9]. This cohort also had a small sample size and there was only one infant who provided a useable week 24 sweat chloride sample, necessitating an ad hoc analysis of sweat chloride change through week 24 utilizing all available measurements from five participants. At day 15 the mean sweat chloride concentration was approximately 30 mmol/L, with all infants with valid results having sweat chloride concentrations below 60 mmol/L. These results suggest



(caption on next page)

Fig. 3. Change from baseline in sweat chloride concentration, fecal elastase-1, IRT, and fecal calprotectin by study visit. (A) Individual values for sweat chloride concentration at BL and each study visit. (B) Mean (SD) absolute change in sweat chloride concentration from BL at each study visit. Six participants did not have sweat chloride measurements at W24: 1 participant discontinued the study at W24 and sample volumes were insufficient for 5 participants. Due to the large number of missing samples at W24, an ad hoc analysis of the average change from BL in sweat chloride through W24 was performed for all post-BL visits. (C) Individual values for fecal elastase-1 at BL and each study visit. Values recorded as ">500" μg/g are displayed as 500 μg/g. Multiple participants had fecal elastase-1 values 500 μg/g at baseline and/or at Day 4; they overlap in the display of the figure. (D) Mean (SD) absolute change in fecal elastase-1 from BL at each study visit. E) Individual values for IRT at BL and each study visit. Values recorded as ">1200 ng/mL" are displayed as 1200 ng/mL. Multiple participants had IRT values of >1200 ng/mL at baseline; they overlap in the display of the figure. (F) Mean (SD) absolute change in IRT from BL at each study visit. (G) Indvidual values for fecal calprotectin at BL and each study visit. (H) Mean (SD) absolute change in fecal calprotectin from BL at each study visit. *Infant discontinued treatment after W9 and discontinued study after W18. †Fecal elastase-1 values >200 μg/g are consistent with pancreatic exocrine sufficiency. ‡The upper limit of normal for fecal calprotectin is 163 μg/g. Abbreviations: BL=baseline; D=day; IRT=immunoreactive trypsinogen; SD=standard deviation; W=week.

that treatment with ivacaftor in infants leads to rapid and clinically meaningful improvement in CFTR function, similar to other cohorts in this study and other studies of ivacaftor in older children, adolescents, and adults [3,4,6,8].

Beyond improvements in CFTR function, ivacaftor treatment also led to improvements in markers of pancreatic function and intestinal inflammation. The mean change in fecal elastase-1 (103.4 μg/g) in infants in this cohort was smaller than changes reported in children aged 4 to less than 6 months (181.0 μg/g) and in children aged 6 to less than 12 months (159.3 μg/g) given ivacaftor [4,6]. Only two of the seven infants in the current cohort were pancreatic insufficient, so the cohort as a whole had better preserved pancreatic function at baseline than those in the older cohorts, as indicated by a higher mean baseline fecal elastase-1 concentration of 344.8 μg/g compared to 184.0 μg/g for infants aged 4 to less than 6 months and 119.6 μg/g for infants aged 6 to less than 12 months. Improvements were also seen in IRT and fecal calprotectin. Taken together with previous cohorts/studies in older children, these results suggest that very early treatment with ivacaftor could slow or even improve exocrine pancreatic damage and intestinal inflammation in infants with CF.

Consistent with the improvements in markers of pancreatic function, infants in the current cohort had improvements in growth parameters, which were in the normal range (but below the median of the reference population [7]) at baseline and remained in the normal range at week 24. While the increases in weight-for-length, weight-for-age z-score, length-for-age z-score, and weight-for-length-for-age z-score were larger than those reported for older children [4,6], early infancy is a developmental period marked by rapid growth changes [10]. Long-term extension studies in infants who initiate ivacaftor early in life may provide further insights into the impact of early treatment initiation on both long-term pancreatic function and growth.

There are limitations to our study. All participants were non-Hispanic white, which reflects the small sample size of the study and the low frequency of eligible disease-causing *CFTR* variants in other ethnic groups [11]. Additionally, the open-label design of the study, which lacked a comparator group, limits interpretation of safety and efficacy outcomes.

5. Conclusions

Ivacaftor treatment was generally safe and well tolerated in this small cohort of seven infants 1 to <4 months of age, though one infant had elevations in liver function >8x the upper limit of normal for which ivacaftor was discontinued. Infants had improvements in CFTR function, pancreatic function, intestinal inflammation, and growth parameters over the 24-week treatment period. Since pharmacokinetics was predictable, an ivacftor dosing regimen in infants 1 to <4 months of age based on weight and age is proposed. Given the small sample size and open-label study design, it will be important to follow infants treated with ivacaftor clinically and in real-world post-approval studies to continue to evaluate safety and efficacy.

Funding

This work was supported by Vertex Pharmaceuticals Incorporated.

Data sharing statement

Vertex Pharmaceuticals Incorporated is committed to advancing medical science and improving patient health. This commitment includes the responsible sharing of clinical study data with qualified researchers. Proposals for the use of these data will be reviewed by a scientific board. Approvals are at the discretion of Vertex Pharmaceuticals Incorporated and will be dependent on the nature of the request, the merit of the research proposed, and the intended use of the data. Please contact CTDS@vrtx.com if you would like to submit a proposal or need more information.

CRediT authorship contribution statement

Paul McNally: Investigation, Writing – review & editing. **Alvin Singh:** Investigation, Writing – review & editing. **Susanna A. McColley:** Investigation, Writing – review & editing. **Jane C. Davies:** Investigation, Writing – original draft, Writing – review & editing. **Mark Higgins:** Conceptualization, Methodology, Validation, Formal analysis, Writing – original draft, Writing – review & editing. **Meng Liu:** Conceptualization, Methodology, Validation, Formal analysis, Writing – review & editing. **Jennifer Lu:** Conceptualization, Methodology, Validation, Formal analysis, Writing – review & editing. **Violeta Rodriguez-Romero:** Conceptualization, Methodology, Validation, Formal analysis, Writing – review & editing. **Judy L. Shih:** Investigation, Writing – review & editing. **Margaret Rosenfeld:** Investigation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

MR has received research grant funding and an advisory board role for Vertex Pharmaceuticals Incorporated for which her institution received payment. AS has received grants/contracts as a principal investigator from Vertex Pharmaceuticals Incorporated. SAM has received compensation to institution as principal investigator and advisory board consulting fees from Vertex Pharmaceuticals Incorporated. PM has received compensation to his institution as co-investigator, advisory board participation, and honoraria for speaker events from Vertex Pharmaceuticals Incorporated. JD has received payment for clinical trial leadership, advisory board participation, and speaker events from Vertex Pharmaceuticals Incorporated. MH, ML, JL, and VR-R are employees of Vertex Pharmaceuticals Incorporated and may own stock or stock options.

Acknowledgments

The authors thank the patients and their families, the study investigators, and the study coordinators for their role in the study. This study was supported by Vertex Pharmaceuticals Incorporated. Medical writing support was provided by Lorilei Richardson, PhD, and Nathan

Blow, PhD, who are employees of Vertex Pharmaceuticals Incorporated and may own stock or stock options in that company. Quality control review was provided under the direction of the authors by Complete HealthVizion, IPG Health Medical Communications, funded by Vertex Pharmaceuticals Incorporated. JCD is supported by the National Institute for Health Research through a Senior Investigator Award, the Imperial Biomedical Research Centre, and the Brompton Clinical Research Facility.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2024.03.012.

References

[1] Van Goor F, Hadida S, Grootenhuis PDJ, Burton B, Cao D, Neuberger T, et al. Rescue of CF airway epithelial cell function in vitro by a CFTR potentiator, VX-770. Proc Natl Acad Sci U S A 2009;106(44):18825–30. https://doi.org/10.1073/pnas.0904709106.

[2] Yu H, Burton B, Huang CJ, Worley J, Cao D, Johnson JP, et al. Ivacaftor potentiation of multiple CFTR channels with gating mutations. J Cyst Fibros 2012;11(3):237–45. https://doi.org/10.1016/j.jcf.2011.12.005.

[3] Accurso FJ, Rowe SM, Clancy JP, Boyle MP, Dunitz JM, Durie PR, et al. Effect of VX-770 in persons with cystic fibrosis and the G551D-*CFTR* mutation. N Engl J Med 2010;363(21):1991–2003. https://doi.org/10.1056/NEJMoa0909825.

[4] Davies JC, Cunningham S, Harris WT, Lapey A, Regelmann WE, Sawicki GS, et al. Safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2–5 years with cystic fibrosis and a *CFTR* gating mutation (KIWI): an open-label, single-arm study. Lancet Respir Med 2016;4(2):107–15. https://doi.org/10.1016/S2213-2600(15)00545-7.

[5] Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Dřevínek P, et al. A CFTR potentiator in patients with cystic fibrosis and the *G551D* mutation. N Engl J Med 2011;365(18):1663–72. https://doi.org/10.1056/NEJMoa1105185.

[6] Rosenfeld M, Wainwright CE, Higgins M, Wang LT, McKee C, Campbell D, et al. Ivacaftor treatment of cystic fibrosis in children aged 12 to <24 months and with a *CFTR* gating mutation (ARRIVAL): a phase 3 single-arm study. Lancet Respir Med 2018;6(7):545–53. https://doi.org/10.1016/S2213-2600(18)30202-9.

[7] Centers for Disease Control and Prevention. WHO growth standards are recommended for use in the U.S. for infants and children 0 to 2 years of age. Available from: https://www.cdc.gov/growthcharts/who_charts.htm#The%20WHO%20Growth%20Charts. [Accessed October 2023].

[8] Davies JC, Wainwright CE, Sawicki GS, Higgins MN, Campbell D, Harris C, et al. Ivacaftor in infants aged 4 to <12 months with cystic fibrosis and a gating mutation. Results of a two-part phase 3 clinical trial. Am J Respir Crit Care Med 2021;203(5):585–93. https://doi.org/10.1164/rccm.202008-3177OC.

[9] Mishra A, Greaves R, Smith K, Carlin JB, Wootton A, Stirling R, et al. Diagnosis of cystic fibrosis by sweat testing: age-specific reference intervals. J Pediatr 2008;153(6):758–63. https://doi.org/10.1016/j.jpeds.2008.04.067.

[10] Bier DM. Growth in the first two years of life. Nestle Nutr Workshop Ser Pediatr Program 2008;61:135–44. https://doi.org/10.1159/000113364.

[11] McGarry ME, McColley SA. Cystic fibrosis patients of minority race and ethnicity less likely eligible for CFTR modulators based on CFTR genotype. Pediatr Pulmonol 2021;56(6):1496–503. https://doi.org/10.1002/ppul.25285.