ORIGINAL ARTICLE

Ivacaftor in Infants Aged 4 to <12 Months with Cystic Fibrosis and a Gating Mutation

Results of a Two-Part Phase 3 Clinical Trial

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Abstract

Rationale: We previously reported that ivacaftor was safe and well tolerated in cohorts aged 12 to <24 months with cystic fibrosis and gating mutations in the ARRIVAL study; here, we report results for cohorts aged 4 to <12 months.

Objectives: To evaluate the safety, pharmacokinetics, and pharmacodynamics of ivacaftor in infants aged 4 to <12 months with one or more gating mutations.

Methods: ARRIVAL is a single-arm phase 3 study. Infants received 25 mg or 50 mg ivacaftor every 12 hours on the basis of age and weight for 4 days in part A and 24 weeks in part B.

Measurements and Main Results: Primary endpoints were safety (parts A and B) and pharmacokinetics (part A). Secondary/tertiary endpoints (part B) included pharmacokinetics and changes in sweat chloride levels, growth, and markers of pancreatic function. Twenty-five infants received ivacaftor, 12 in part A and 17 in part B (four infants participated in both parts). Pharmacokinetics was consistent with that in older groups. Most adverse events were mild or moderate. In part B, cough was the most common adverse event ($n = 10$ [58.8%]). Five infants (part A, $n = 1$ [8.3%]; part B, $n = 4$ [23.5%]) had serious adverse events, all of which were considered to be not or unlikely related to ivacaftor. No deaths or treatment discontinuations occurred. One infant (5.9%) experienced an alanine transaminase elevation >3 to ≤5× the upper limit of normal at Week 24. No other adverse trends in laboratory tests, vital signs, or ECG parameters were reported. Sweat chloride concentrations and measures of pancreatic obstruction improved.

Conclusions: This study of ivacaftor in the first year of life supports treating the underlying cause of cystic fibrosis in children aged ≥4 months with one or more gating mutations.

Clinical trial registered with clinicaltrials.gov (NCT02725567).

Keywords: CFTR potentiator; pancreatic function; pharmacokinetics; safety

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Data sharing statement: Vertex is committed to advancing medical science and improving the health of people with cystic fibrosis. This includes the responsible sharing of clinical trial 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 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.

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At a Glance Commentary

Scientific Knowledge on the Subject: Exocrine pancreatic dysfunction and structural lung disease in cystic fibrosis (CF) are evident in infancy. The clinical benefits of ivacaftor, a small-molecule potentiator of CFTR (CF transmembrane conductance regulator) function, have been established in children and adults with CF and gating mutations. Findings in young children suggest that early intervention with CFTR modulators may delay or slow the progression of exocrine pancreatic insufficiency and impaired growth. We previously reported that ivacaftor was safe and well tolerated in cohorts aged 12 to <24 months with CF and gating mutations in the single-arm, phase 3 ARRIVAL study.

What This Study Adds to the Field: Here, we report results from infants aged 4 to <12 months in the ARRIVAL study. Our findings are consistent with observations in older children and suggest that ivacaftor can be dosed safely in infants ≥4 months of age. The safety profile of ivacaftor was consistent with its established safety profile. Substantial improvements in sweat chloride concentrations indicate improved CFTR function. Improvements in markers of pancreatic function suggest the potential of ivacaftor to delay or minimize progressive exocrine pancreatic dysfunction. This study supports treating the underlying cause of CF in children aged ≥4 months.

Cystic fibrosis (CF) is a life-shortening autosomal recessive disorder characterized by progressive disease manifestations beginning at an early age (1, 2). CF is caused by absent or defective CFTR (CF transmembrane conductance regulator) protein, resulting from mutations in the *CFTR* gene (1). CFTR is an anion transporter responsible for conductance of chloride and bicarbonate across the apical membrane of epithelial cells (1). Failure to regulate chloride transport results in the multisystem pathology associated with CF, including obstructive lung disease, pancreatic insufficiency, and intestinal abnormalities, all of which contribute to reduced quality of life, significant lifetime morbidity, and reduced life expectancy (1). Reduced ion transport in the lungs leads to a cycle of mucus buildup, inflammation, and infection, which causes progressive lung damage and eventual loss of lung function, the most common cause of mortality in people with CF (1, 3, 4). Airway infection and structural lung disease are evident in infancy (1, 5). Reduced CFTR activity in the pancreas causes obstruction of intrapancreatic ducts that destroys exocrine tissue, leading to pancreatic insufficiency that results in gastrointestinal malabsorption (6). Pancreatic insufficiency and poor nutritional status are the most significant clinical manifestations of CF in infants (6–8). Approximately 85% of infants with CF are born with or develop exocrine pancreatic insufficiency within the first year of life (6).

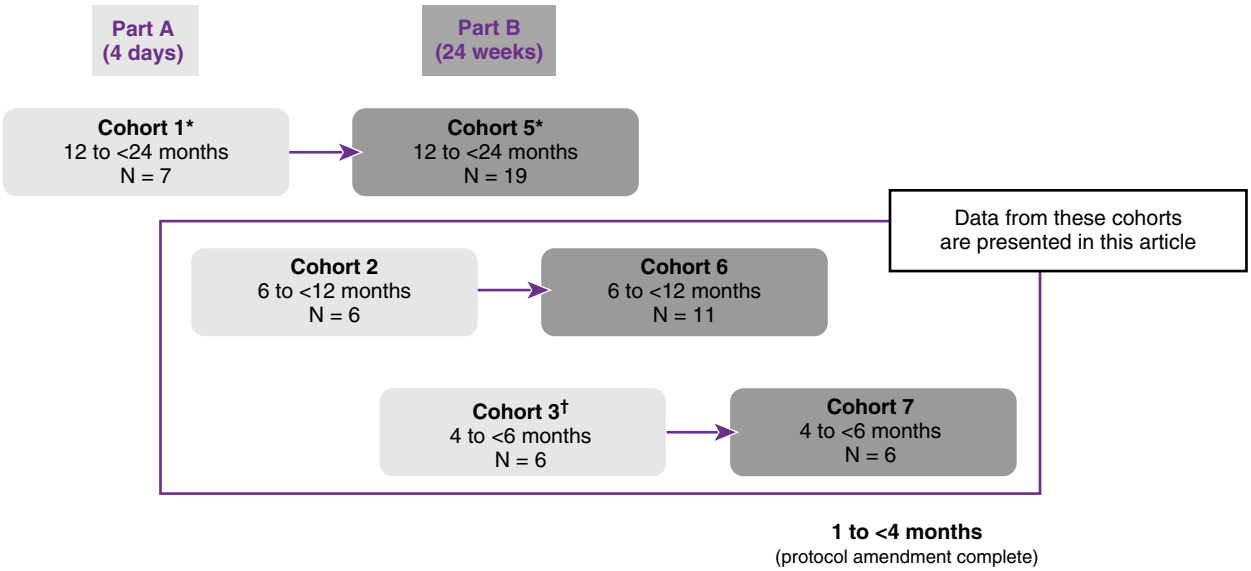
Ivacaftor is a small-molecule potentiator of CFTR function that acts by increasing protein channel gating to enhance chloride transport in wild-type and multiple mutant CFTR forms *in vitro*, including the G551D mutation and others (9–11). The clinical benefits of ivacaftor, including improvements in lung function and nutritional status, have been established in children and adults with CF (9, 12–16). In addition, in children 1–5 years of age, ivacaftor has led to improvements in biomarkers of exocrine pancreatic function (13, 16, 17).

Exocrine pancreatic organ damage, commencing *in utero*, was historically believed to be irreversible (18). Studies across different populations have demonstrated elevations in FE-1 (fecal elastase-1), a marker of exocrine pancreatic function, and reductions in IRT (immunoreactive trypsinogen), a marker of pancreatic insult, with CFTR modulators (13, 16, 17, 19–21). These findings suggest that early intervention with CFTR modulators may delay or slow the progression of exocrine pancreatic insufficiency and impaired growth (13, 16, 17, 21). The widely established practice of newborn screening (22) provides an opportunity for early therapeutic intervention with ivacaftor.

Promising data with CFTR modulators support the use of modulators for pediatric populations; however, interventions in this vulnerable age group need to be carefully evaluated in terms of pharmacokinetics and safety. ARRIVAL is a single-arm, phase 3 study designed to evaluate the safety, pharmacokinetics, and pharmacodynamics of ivacaftor in children <24 months of age. Results in children aged 12 to <24 months have been previously reported (16). Here, we report findings in infants aged 4 to <12 months. Some of the results from these cohorts have been previously reported in the form of abstracts (23–25).

Methods

ARRIVAL (NCT02725567) is an ongoing phase 3, multicenter, single-arm, two-part study. A list of study sites and investigators is provided in Table E1 in the online supplement. Children are enrolled sequentially into three age groups: *1*) 12 to <24 months (already reported) (16), *2*) 6 to <12 months, and *3*) <6 months (Figure 1); groups *2* and *3* are reported together here. Given the high plasma drug concentrations seen in one infant aged 3 months in part A (described in this report), the lower age limit of part B was adjusted to 4 months, and younger infants will be evaluated separately under an amended ARRIVAL study protocol. Infants could participate in one or both parts (16). Enrollment in part B began after the pharmacokinetic data for the corresponding part A cohort were reviewed and the dose was confirmed; to ensure that ivacaftor exposure was maintained within the targeted range, age and weight requirements for the 4- to <6-month cohort were implemented in part B. The primary endpoints of part A were the safety and pharmacokinetics of ivacaftor and its metabolites after 4 days of treatment. The primary endpoint of part B was safety as determined over 24 weeks by adverse events (AEs), clinical laboratory assessments, vital signs, ECGs, and physical and ophthalmologic examinations. Secondary endpoints in part B were pharmacokinetics and absolute change from baseline in sweat chloride concentration at 24 weeks as a pharmacodynamic assessment. Tertiary objectives in part B included the evaluation of the efficacy of ivacaftor on the basis of change from baseline in measures of growth, markers of pancreatic function and inflammation, and lung clearance index ($LCI_{2.5}$). Measurement of $LCI_{2.5}$ was an optional procedure at one site.



Part A: Enrollment in each subsequent cohort began after safety and PK data were reviewed from the previous cohorts meeting prespecified parameters.

Part B: Enrollment in each cohort began after safety and PK data were reviewed from the corresponding cohort in part A to confirm the dose, and the 24-week safety data of the previous cohort in part B were reviewed.

	4 to <6 Months†		6 to <12 Months	
	5 to <7 kg	7 to <14 kg	5 to <7 kg	7 to <14 kg
Part A	25 mg q12h	50 mg q12h	25 mg q12h	50 mg q12h
Part B	25 mg q12h‡		25 mg q12h	50 mg q12h

Figure 1. Cohorts in the ARRIVAL study and ivacaftor dosing based on age and weight. *Data from cohorts 1 and 5 were reported previously (16). †Two infants in cohort 3 of part A were aged 3 months. ‡If an infant reached age 6 months during the study, dosing was switched to weight-based dosing. PK = pharmacokinetics; q12h = every 12 hours. Reprinted by permission from Reference 16.

Eligible infants were aged <12 months at the time of treatment initiation (Day 1) with a confirmed diagnosis of CF and a *CFTR* gating mutation (*G551D*, *G551S*, *G178R*, *S549N*, *S549R*, *G1244E*, *S1251N*, *S1255P*, or *G1349D*) on one or more alleles. Infants with an *R117H* mutation were also eligible (U.S. sites only). Full inclusion criteria have been described previously (16). Ivacaftor was supplied as a granule formulation, and doses were based on age and weight (Figure 1). Caregivers were instructed to administer ivacaftor orally every 12 hours at the same times each day.

The sample size of five or more infants in part A and five or more infants in part B for each of the two age groups (6 to <12 mo and 4 to <6 mo) was based on the predicted availability of the participant population and pharmacokinetic analysis considerations. Pharmacokinetic and safety analyses included all infants who received at least one dose of study drug. Pharmacodynamic and exploratory efficacy analyses were applicable to part B only. The study was not powered to detect particular treatment effects, and all analyses were descriptive. Changes from baseline were assessed in infants with paired data available at baseline and 24 weeks. Prespecified analyses were separated by age cohort (6 to <12 mo and <6 mo); all pooled results combining data for 4 to <12 months were *post hoc*. Additional details are provided in the online supplement.

Results

Baseline Characteristics and Demographics

Twelve infants aged 3 to <12 months enrolled in part A and completed dosing, four at a dose of 25 mg ivacaftor twice daily and eight at a dose of 50 mg ivacaftor twice daily (Figure E1). Baseline characteristics and demographics of infants in the part A cohort are shown in Table E2. Four infants who completed part A also participated in part B. Seven of the remaining eight infants who participated in part A aged out and were not eligible to participate in part B. The additional infant was screened for the extension study instead of screening for part B. Seventeen infants were enrolled in and completed part B, of whom six received 25 mg ivacaftor twice daily and eleven received 50 mg ivacaftor twice daily on Day 1. Fifteen infants in part B had a *G551D* mutation on one allele, and one infant each had a *G178R* or an *R117H-5T* mutation on one allele (Table 1). At the end of part B, all 17 infants continued into an extension study (Figure E1).

Pharmacokinetics

Modeled area under the curve (AUC) and minimum plasma drug concentrations derived from pharmacokinetic data

indicated that drug exposures in infants aged 4 to <12 months were consistent with those observed in older children and adults (Table E3). There were no high plasma drug concentrations or exposures beyond the range of prior clinical experience. However, among the two infants aged 3 months enrolled in part A, one (weighing 6.0 kg), who received 25 mg ivacaftor twice daily, had an AUC value greater than the 95th percentile of that observed in the adult population but within the range of prior clinical experience; the AUC exposure from the additional infant aged 3 months was within the targeted range between the fifth and 95th percentiles of the adult population. As a result, a dose justification memo was issued such that participants in part B were required to be 4 to <6 months of age, weighing ⩾5 kg on study Day 1, and were administered 25 mg ivacaftor every 12 hours regardless of weight. Infants younger than those presently studied are being evaluated in an amended protocol that will be reported separately.

Safety

In part A, 7 of 12 infants (58.3%) had one or more treatment-emergent AEs (TEAEs). The majority of infants had AEs that were mild or moderate and considered not or unlikely to be related to the study drug. One event each of constipation, vomiting, and sleep disorder were considered to be possibly related to the study drug. One infant, aged 4 months, had a severe TEAE of thrombocytopenia (platelet count, 44×10^9/L) that was noted at Day 5 and reported as a serious AE (SAE). The investigator suspected omeprazole to be the causal agent for the thrombocytopenia. Platelet concentration in this infant returned to normal approximately 1 month after discontinuation of omeprazole, and the TEAE was considered resolved. No other SAEs were reported in part A. There were no life-threatening AEs and no deaths or treatment discontinuations in part A.

In part B, 16 of 17 infants (94.1%) had one or more TEAEs (Table 2). The majority of infants had AEs that were mild or moderate and considered not or unlikely to be related to the study drug. The most common TEAEs were cough, pyrexia, rhinorrhea, nasal congestion, and vomiting. One infant had a severe TEAE of bronchiolitis (reported as an SAE) that was considered not or unlikely to be related to the study drug. Two other infants had severe TEAEs (reported as SAEs) of a viral respiratory tract infection and a viral rash that were also considered not or unlikely to be related to the study drug. SAEs occurred in 4 of 17 infants (23.5%; bronchiolitis [noted above], cough, viral respiratory tract infection [noted above], and viral rash [noted above]; $n = 1$ each). All SAEs were considered not or unlikely to be related to the study drug. There were no life-threatening AEs and no deaths or treatment discontinuations. One infant experienced a single ALT (alanine transaminase) elevation of >3 to ⩽5× upper limit of normal at Week 24, without bilirubin elevation (Table E4). The infant completed the study and enrolled in the extension study before the elevated ALT result being available; the ALT subsequently returned to normal without change in study drug dosing. No cataracts were observed, and there were no other notable adverse trends in laboratory tests, vital signs, or ECG parameters.

Pharmacodynamics

Nine infants had paired sweat chloride values available at baseline and Week 24; mean (SD) absolute change from baseline at Week 24 was −55.7 (16.2) mmol/L (Table 3). Individual decreases in sweat chloride concentrations ranged from −31.0 to −73.5 mmol/L. At the end of the study, the mean (SD) sweat chloride concentration (measured in nine infants) was 41.3 (15.9) mmol/L; in one infant, it was 24.0 mmol/L (Table 3 and Figure E2). Concentrations of <30.0 mmol/L, consistent with normal CFTR function (26), were obtained at least once during the study in 3 of 17 infants (17.6%) (Figure E2). Age-based cohort findings are shown in Figure 2.

Efficacy

Among the 13 infants with paired measurements of FE-1 concentration, the mean (SD) absolute change from baseline at Week 24 was 166.0 (140.6) μg/g (Table 3).

Table 1. Baseline Characteristics and Demographics in the Part B Cohorts

	4 to <6 mo (*N* = 6)	6 to <12 mo (*N* = 11)	Total 4 to <12 mo* (*N* = 17)
Age at baseline/Day 1, mo, mean (SD)	4.5 (0.55)	9.0 (1.34)	7.4 (2.48)
Sex, M, *n* (%)	5 (83.3)	2 (18.2)	7 (41.2)
Weight at baseline/Day 1, kg, mean (SD)	6.9 (0.7)	8.9 (1.0)	8.2 (1.3)
Weight-for-age *z*-score, mean (SD)	−0.65 (0.98)	0.37 (0.71)	0.01 (0.93)
Length-for-age *z*-score, mean (SD)	−0.12 (1.71)	0.63 (0.62)	0.36 (1.14)
Weight-for-length-for-age *z*-score, mean (SD)	−0.66 (0.97)	0.13 (0.85)	−0.15 (0.95)
Race, white, *n* (%)	6 (100)	11 (100)	17 (100)
Geographical region, *n* (%)			
North America	4 (66.7)	7 (63.6)	11 (64.7)
Europe	2 (33.3)	3 (27.3)	5 (29.4)
Australia	0 (0)	1 (9.1)	1 (5.9)
Genotype, *n* (%)			
G551D/F508del	4 (66.7)	9 (81.8)	13 (76.5)
G551D/N1303K	1 (16.7)	0 (0)	1 (5.9)
G551D/S108F	0 (0)	1 (9.1)	1 (5.9)
G178R/F508del	0 (0)	1 (9.1)	1 (5.9)
R117H-5T/F508del	1 (16.7)	0 (0)	1 (5.9)

*Pooled results from a *post hoc* analysis.

Table 2. TEAEs in the Part B Cohorts (Occurring in Two or More Infants in the Pooled Cohort)

Preferred Term	4 to <6 mo (*N* = 6)	6 to <12 mo (*N* = 11)	Total 4 to <12 mo* (*N* = 17)
Infants with ⩾1 TEAE	6 (100.0)	10 (90.9)	16 (94.1)
Cough	3 (50.0)	7 (63.6)	10 (58.8)
Pyrexia	2 (33.3)	3 (27.3)	5 (29.4)
Rhinorrhea	1 (16.7)	4 (36.4)	5 (29.4)
Nasal congestion	0 (0)	4 (36.4)	4 (23.5)
Vomiting	1 (16.7)	3 (27.3)	4 (23.5)
Otitis media	1 (16.7)	2 (18.2)	3 (17.6)
Upper respiratory tract infection	2 (33.3)	1 (9.1)	3 (17.6)
Constipation	1 (16.7)	1 (9.1)	2 (11.8)
Dermatitis diaper	0 (0)	2 (18.2)	2 (11.8)
Ear infection	0 (0)	2 (18.2)	2 (11.8)
Hand, foot, and mouth disease	0 (0)	2 (18.2)	2 (11.8)
Tonsillitis	0 (0)	2 (18.2)	2 (11.8)
Viral upper respiratory tract infection	0 (0)	2 (18.2)	2 (11.8)

Definition of abbreviation: TEAE = treatment-emergent adverse event.
Data are given as *n* (%).
*Pooled results from a *post hoc* analysis.

Eleven of the 15 infants (73.3%) with baseline measurements had values consistent with pancreatic insufficiency (⩽200 μg/g) (27). Nine of these 11 infants also had results at 24 weeks, seven (77.8%) of whom demonstrated FE-1 concentrations of >200 μg/g. The four infants with FE-1 concentrations of >200 μg/g at baseline maintained FE-1 in this range after 24 weeks of ivacaftor treatment. FE-1 concentrations increased to >200 μg/g at least once during the study in 15 of 17 infants (88.2%) (Figure E3). Age-based cohort findings are shown in Figure 3.

Mean (SD) absolute change from baseline in IRT concentration (assessed in 11 infants with paired data available) was −474.5 (369.8) ng/ml at Week 24 (Table 3); notably, 13 of the 14 infants (92.9%) with measurements at baseline had mean IRT values at the upper limit of quantification of the assay (1,200.0 ng/ml). Age-based cohort findings for IRT are shown in Figure E4. Mean (SD) absolute changes from baseline in lipase and amylase at Week 24 were −247.2 (241.7) U/L and −17.8 (35.8) U/L, respectively (Table 3). Reductions in mean lipase concentrations were observed at Day 5 in part A and by Week 2 and sustained through Week 24 in part B. Age-based cohort findings for lipase and amylase are shown in Figure E5.

Growth parameters were maintained during the study (Table 3). Age-based cohort findings for growth parameters are shown in Figure E6. The optional $LCI_{2.5}$ was measured in only one infant (online supplement). All infants accepted and fully consumed the dose of ivacaftor assessed for palatability (online supplement).

Discussion

Ivacaftor given at 25 mg or 50 mg every 12 hours was generally safe and well tolerated in infants aged 4 to <12 months with *CFTR* gating mutations. The pharmacokinetics of ivacaftor in infants aged 4 to <12 months were similar to those in older children and adults with CF and confirmed that ivacaftor can be safely administered to this age group. Because one infant aged 3 months had an AUC exposure above the adult 95th percentile, we will study ivacaftor dosing in additional participants aged <4 months before making dosing recommendations for that age range. The data presented here in infants aged 6 to <12 months supported an indication approval for ivacaftor use in that age group (28, 29).

The safety profile of ivacaftor over 24 weeks in part B was similar to that reported in older children (9, 12–14, 16). The TEAEs reported in infants aged 4 to <12 months were mostly typical for young children with CF and were consistent with those previously reported in ARRIVAL cohorts aged 12 to <24 months (16). All SAEs were judged to be not related or unlikely to be related to ivacaftor. No infant discontinued treatment because of an AE or any safety findings. Rates of liver function test elevations appeared lower than those previously reported in the ARRIVAL (children aged 12 to <24 mo) and KIWI (children aged 2–5 yr) studies (13, 16), with only one infant aged 4 to <12 months experiencing a transaminase elevation. There were no life-threatening AEs and no deaths. No cataracts were observed, and there were no other notable adverse trends in laboratory tests, vital signs, or ECG parameters.

This study demonstrated improvements in biomarkers of CFTR activity. Substantial decreases in sweat chloride concentration were seen, which is a measure of CFTR function. Although the sample sizes were small, the mean improvement in sweat chloride concentration of −55.7 (SD, 16.2) mmol/L in these infants aged 4 to <12 months appears comparable with what has been reported in older children (mean [SD] absolute change from baseline at 24 wk was −73.5 [17.5] and −46.9 [26.2] mmol/L in ARRIVAL and KIWI, respectively) (13, 16). Sweat chloride concentrations ⩾60 mmol/L are diagnostic for CF, whereas 30–59 mmol/L indicates residual CFTR function, and <30 mmol/L suggests that CF is unlikely (26). The mean (SD) sweat chloride concentration at Week 24 in this study was 41.3 (15.9) mmol/L and was <30 mmol/L at least once during the study in three infants, demonstrating a robust effect of ivacaftor on CFTR function in these very young infants.

Because pancreatic damage begins before birth and progresses during

Table 3. Changes from Baseline to Week 24 in Secondary and Tertiary Endpoints in the Part B Cohorts

	Sweat Chloride Concentration (*mmol/L*)*†	Weight-for-Age *z*-Score‡	Length-for-Age *z*-Score‡	Weight-for-Length-for-Age *z*-Score‡	FE-1 Concentration (*μg/g*)‡§	IRT Concentration (*ng/ml*)‡‖	Lipase Concentration (*U/L*)¶**	Amylase Concentration (*U/L*)¶††
4 to <6 mo								
Baseline value, mean (SD)	97.4 (16.4); *n* = 6	−0.65 (0.98); *n* = 6	−0.12 (1.71); *n* = 6	−0.66 (0.97); *n* = 6	184.0 (190.8); *n* = 5	1,200.0 (0.0)‡‡; *n* = 5	308.8 (168.3); *n* = 6	69.2 (30.3); *n* = 6
Value at Week 24, mean (SD)	37.7 (2.9); *n* = 3	0.18 (0.97); *n* = 6	0.44 (1.59); *n* = 6	0.02 (0.53); *n* = 6	398.3 (117.5); *n* = 4	724.9 (438.2); *n* = 5	50.2 (33.0); *n* = 6	58.8 (27.4); *n* = 6
Absolute change,§§ mean (SD)	−50.0 (17.3); *n* = 3	0.82 (0.54); *n* = 6	0.56 (0.86); *n* = 6	0.68 (1.12); *n* = 6	181.0 (122.9); *n* = 4	−593.8 (402.5); *n* = 4	−258.7 (158.4); *n* = 6	−10.3 (37.2); *n* = 6
6 to <12 mo								
Baseline value, mean (SD)	101.5 (9.8); *n* = 11	0.37 (0.71); *n* = 11	0.63 (0.62); *n* = 11	0.13 (0.85); *n* = 11	119.6 (199.1); *n* = 10	1,120.6 (238.2); *n* = 9	331.4 (286.5); *n* = 11	76.1 (39.8); *n* = 11
Value at Week 24, mean (SD)	43.1 (19.8); *n* = 6	0.73 (0.75); *n* = 11	0.89 (1.2); *n* = 11	0.40 (1.25); *n* = 11	291.3 (170.5); *n* = 9	753.2 (363.6); *n* = 9	90.5 (63.8); *n* = 11	54.2 (29.0); *n* = 11
Absolute change§§, mean (SD)	−58.6 (16.5); *n* = 6	0.36 (0.54); *n* = 11	0.27 (1.34); *n* = 11	0.26 (1.30); *n* = 11	159.3 (154.4); *n* = 9	−406.2 (363.3); *n* = 7	−240.9 (284.2); *n* = 11	−21.9 (36.1); *n* = 11
4 to <12 mo‖‖								
Baseline value, mean (SD)	100.1 (12.2); *n* = 17	0.01 (0.93); *n* = 17	0.36 (1.14); *n* = 17	−0.15 (0.95); *n* = 17	141.0 (192.0); *n* = 15	1,149.0 (191.0); *n* = 14	323.4 (245.5); *n* = 17	73.6 (35.9); *n* = 17
Value at Week 24, mean (SD)	41.3 (15.9); *n* = 9	0.53 (0.85); *n* = 17	0.73 (1.32); *n* = 17	0.26 (1.05); *n* = 17	324.2 (159.6); *n* = 13	743.1 (375.0); *n* = 14	76.2 (57.2); *n* = 17	55.8 (27.6); *n* = 17
Absolute change, mean (SD; 95% CI)§§	−55.7 (16.2; −68.2 to −43.3); *n* = 9	0.52 (0.57; 0.23 to 0.82); *n* = 17	0.37 (1.17; −0.23 to 0.97); *n* = 17	0.41 (1.22; −0.22 to 1.04); *n* = 17	166.0 (140.6; 81.0 to 250.9); *n* = 13	−474.5 (369.8; −722.9 to −226.0); *n* = 11	−247.2 (241.7; −371.4 to −122.9); *n* = 17	−17.8 (35.8; −36.2 to 0.6); *n* = 17

Definition of abbreviations: FE-1 = fecal elastase-1; IRT = immunoreactive trypsinogen.

*Normal range <30 mmol/L.

†Secondary endpoint.

‡Tertiary endpoint.

§Pancreatic exocrine insufficiency ⩽200 μg/g; 11 infants had baseline concentrations of ⩽200 μg/g, of whom nine had paired data at baseline and Week 24 and seven had concentrations of >200 μg/g at Week 24. Four infants had baseline FE-1 values of >200 μg/g at baseline and remained >200 μg/g throughout the study.

‖Reference range not established but reduction in concentration indicates improvement (16).

¶Safety assessment.

**Normal range, 4–29 U/L (<6 mo) or 4–23 U/L (6 to <12 mo).

††Normal range, 1–17 U/L (<6 mo) or 6–44 U/L (6 to <12 mo).

‡‡The highest concentration threshold for IRT is 1,200.0 ng/ml.

§§Calculated from the infants with data available at both time points.

‖‖Pooled results from a *post hoc* analysis.

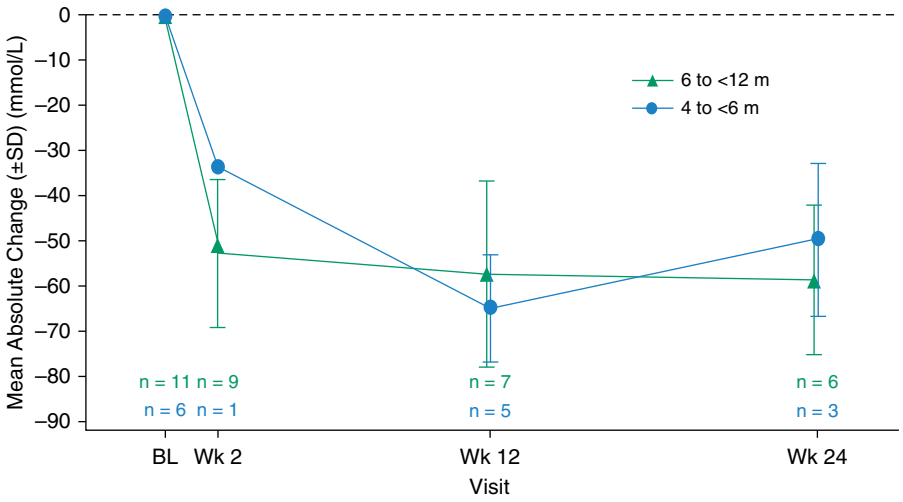


Figure 2. Mean absolute change from baseline in sweat chloride concentration. The mean (SD) sweat chloride value at baseline was 97.4 (16.4) mmol/L in infants aged 4 to <6 months and was 101.5 (9.8) mmol/L in infants aged 6 to <12 months. BL = baseline.

infancy (6, 7), CFTR modulators used early in life have the potential to alter the natural progression of CF. In older children in the ARRIVAL and KIWI studies, improvements in concentrations of FE-1, a biomarker of exocrine pancreatic function, were seen from baseline to 24 weeks (mean [SD] increases of 164.7 [151.9] μg/g and 99.8 [138.4] μg/g in ARRIVAL and KIWI, respectively) (13, 16). Similarly, in the current report, mean (SD) improvement in FE-1 concentrations at Week 24 was 166.0 (140.6) μg/g. Eleven infants had baseline FE-1 concentrations of ≤200 μg/g, indicating pancreatic insufficiency, among whom seven of nine with paired data had regained pancreatic sufficiency at Week 24. Although the reduction in IRT concentrations reported here was not as robust as that previously reported in the older ARRIVAL cohort (16), nearly all infants aged 4 to <12 months had mean baseline IRT values at the upper limit of quantification of the assay (1,200.0 ng/ml). Consistent with this, IRT concentrations are typically elevated in infants with CF (30); thus, rapid decreases in IRT because of ivacaftor may have gone undetected in our study because they remained greater than the upper limit of quantitation. We previously reported substantial decreases in concentrations of IRT by Week 2 in the ARRIVAL cohort aged 12 to <24 months (16).

Lipase and amylase concentrations were collected as part of safety assessments and provide additional insight into pancreatic function because high concentrations of these enzymes are associated with pancreatic inflammation or insult (31). Lipase values in infants aged 4 to <12 months were similar to those reported in the ARRIVAL cohort aged 12 to <24 months; in both age groups, reductions in lipase concentrations were seen after just 4 days of treatment in part A of the study (16). Amylase results in infants aged 4 to <12 months were variable compared with results seen in older children, with mean (SD) absolute changes from baseline in amylase at Week 24 of −17.8 (35.8) U/L in the current report and −54.8 (70.5) U/L in the ARRIVAL cohort aged 12 to <24 months (16). Notably, the fraction of pancreatic amylase isoenzyme activity is ∼4% of the total activity in newborns but rises to ∼45% of the total activity in adults (32). In contrast, the fraction of salivary-like amylase isoenzyme activity is ∼89% of the total activity in newborns and ∼56% of the total activity in adults (32). Because fractionation of amylase into pancreatic and salivary components was not performed, changes in pancreatic amylase may have gone undetected in the current study due to the relatively high fraction of salivary amylase expected in this age group.

Although the clinical relevance of improvements in biomarkers of pancreatic function is unknown, the combined findings in children aged 4 to <24 months in ARRIVAL and aged 2–5 years in KIWI suggest a possible positive and protective effect of ivacaftor on pancreatic exocrine function early in life.

At baseline, infants were generally well nourished, with normal weight and length *z*-scores, and growth parameters were maintained over the course of the study. In the current study, aside from the measurement of $LCI_{2.5}$ in one infant, we did not perform assessments of lung function because of the challenges of evaluating lung function in infants.

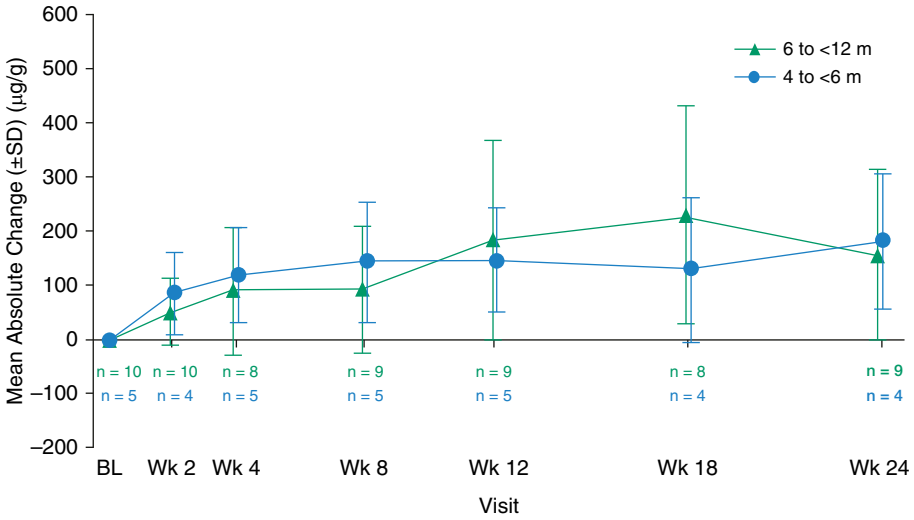


Figure 3. Mean absolute change from baseline in FE-1 (fecal elastase-1) concentration. BL = baseline.

Limitations of this study include the small sample size and the single-arm study design, both reflecting the rarity of these mutations in CF and small population of children this age with CF. The single-arm design without a comparator group limits the interpretation of safety endpoints and clinical outcomes. Further data in these participants will accrue during the extension 770–126 study (NCT03277196). The ARRIVAL study will continue to assess the pharmacokinetics and safety of ivacaftor in infants <4 months.

Conclusions

This study of CFTR modulation in the first year of life suggests that ivacaftor can be safely administered to infants ⩾4 months of age. Our findings are consistent with observations in older children and support treating the underlying cause of CF in children ⩾4 months. Ivacaftor has a favorable safety profile; it was well tolerated at both doses tested, with no new safety concerns. Results of this study suggest improvements in CFTR function, no adverse effects on growth, and reductions in lipase concentrations with ivacaftor. Improvements in FE-1 and IRT concentrations (together with lipase data) support the potential of ivacaftor to delay or possibly minimize progressive exocrine pancreatic dysfunction. Studies evaluating a larger number of children for longer periods of time are needed to further test this hypothesis. Studies of pharmacokinetics and safety in younger infants are planned. ■

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