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Original Article

A phase I study assessing the safety and tolerability of SPL84, an inhaled antisense oligonucleotide for treatment of cystic fibrosis patients with the 3849 +10kb C->T

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ABSTRACT

Background: Antisense Oligonucleotides (ASOs) are small synthetic nucleic acid molecules able to bind specific sequences within target Ribonucleic Acid (RNA) molecules. SPL84 is an ASO drug developed for treatment of cystic fibrosis (CF) patients carrying the 3849 + 10 kb C->T Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*) splicing mutation. The 3849 + 10 kb C->T variant leads to inclusion of cryptic exon harboring stop codon leading to the production of truncated non-functional *CFTR* proteins. *in vitro*, SPL84 treatment results in splicing modulation, which leads to an increase of correctly spliced *CFTR* RNA and higher levels of functional *CFTR* proteins.

Methods: SPL84 was tested in a blinded, placebo-controlled phase 1 study in thirty two (32) healthy volunteers (HVs), each received a single dose of either SPL84 or placebo by inhalation. A total of 8 participants were randomized to each of the 4 escalating cohorts in a 3:1 ratio (active: placebo). Safety and tolerability were evaluated by monitoring adverse events (AEs), vital signs, physical exam findings, spirometry, electrocardiograms (ECG), and analyses of safety laboratories. Blood samples were obtained periodically over 24 h for measurement of systemic exposure.

Results: There were no significant changes from baseline in vital signs, clinical laboratory values, ECG, physical examination, or pulmonary function. There were no Serious Adverse Events (SAEs) in the study, and there were no significant adverse events. The systemic exposure to SPL84 was low and tended to be dose dependent. The exposure, expressed in terms of area under the curve to infinity (AUC_{inf}), at the no observed adverse effect level (NOAEL) in 9-week toxicological mice study was 7.51 μg/ml*hrs, which is ~20 times higher than the exposure at the 160 mg dose (444 ng/ml*hrs).

Conclusions: SPL84 was safe and well-tolerated when administered as a single inhaled dose to HVs at doses up to 160 mg, with minimal systemic exposure. There were no safety issues observed, no SAEs, no significant related AEs, and, importantly, no significant effect on pulmonary function. The successful completion of the study enabled the initiation of multi-dosing of CF patients in a phase 2 clinical study.

1. Background

Cystic fibrosis (CF) is the most common life shortening autosomal recessive disorder among the European-American population. There are estimated 160,000 people with CF (pwCF) worldwide [1], with currently a median survival of ~50 years for an individual with CF in the United States .

CF is caused by mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene, leading to absence or dysfunction of the CFTR protein, which regulates ion transport across the apical membrane at the surface of epithelia cells of the exocrine system [2,3]. Although CFTR functions mainly as a chloride channel, it has many other regulatory roles, including inhibition of sodium transport through the epithelial sodium channel, regulation of the outwardly rectifying

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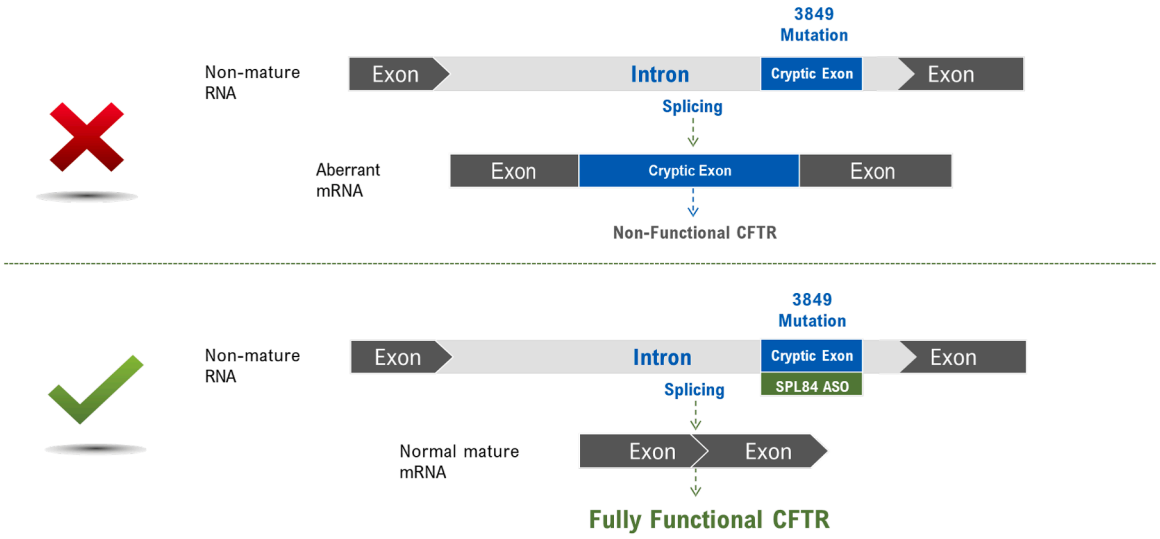

Fig. 1. Effect of 3849 + 10 kb C->T Mutation on CFTR Transcript and SPL84 ASO Mode of Action.

chloride channel, regulation of Adenosine Triphosphate (ATP) channels, regulation of intracellular vesicle transport, acidification of intracellular organelles, and inhibition of endogenous calcium-activated chloride channels [4].

In the lungs, *CFTR* dysfunction leads to airway surface liquid depletion and thickened and viscous mucus that adheres to airway surfaces. The result is decreased mucociliary clearance and impaired host defenses. Dehydrated, thickened and tenacious secretions lead to endobronchial infections with a limited spectrum of distinctive bacteria and an exaggerated inflammatory response, leading to development of bronchiectasis and progressive obstructive airways disease. Pulmonary insufficiency is responsible for most CF-related deaths [5,6].

Since CF is an autosomal recessive disorder, subjects with a single working copy are carriers and otherwise healthy. Subjects with CF can bear the same variant (homozygotes) or different *CFTR* variants on each allele. Over 2000 changes were reported in the *CFTR* gene (Toronto *CFTR* variant database), and more than 700 mutations are known to cause disease most of them are rare [7].

The most common CF variant is F508del, which occurs in ~85% of CF patients. Among all the identified mutations in the *CFTR* gene, 10–15% affect the correct splicing of the gene transcripts. These include non-canonical splicing mutations that generate both aberrant and correct splicing of the *CFTR* gene, such as: 3849+10 kb C->T (c.3717+12191C->T), 2789+5 G->*A* (c.2657+5G->*A*), 1811+1.6 kb A->*G* (c.1679+1634A->*G*) and 3272–26A->*G* (c.3140–26A->*G*). These variants are classified as class V variants (variants that to reduced amounts of normal *CFTR* proteins at the cell surface). These variants are associated with extensive variation in disease severity, ranging from severe typical CF to a milder disease, with most of the patients demonstrating pancreatic sufficiency. However, the lung disease severity and the rate of *Pseudomonas aeruginosa* infection is similar to that of severe CF patients [8,9].

The 3849 + 10 kb C->T *CFTR* splicing variant generates an aberrant 5′ splice site deep in intron 22 of the *CFTR* pre-mRNA and activates a cryptic 3′ splice site 84 nucleotides upstream, resulting in the inclusion of 84 intronic nucleotides as a cryptic exon in the *CFTR* mRNA [10]. This 84 base pair (bp) cryptic exon contains an in-frame stop codon that leads to degradation of a significant fraction of the mRNA by the Nonsense Mediated Decay (NMD) mechanism as well as to the production of truncated non-functional *CFTR* proteins [11,12] (Fig. 1).

Although elexacaftor-tezacaftor-ivacaftor and other CFTR modulators (ivacaftor or tezacaftor-ivacaftor) have some effect in restoring CFTR function in people with this splicing variant, as recently reported [13], SPL84 is a specific ASO utilizing a novel mechanism of action (Fig. 1) that aims to correct the splicing defect in the *CFTR* gene, caused by the 3849 + 10Kb C->T variant. SPL84 is aimed at suppressing the inclusion of the 84 bp cryptic exon in the *CFTR* pre-mRNA, resulting in the production of normal, fully functional *CFTR* protein instead of a truncated, dysfunctional one. This can potentially improve the patient's lung function, clinical condition, and quality of life (Fig. 1).

In previous publications, SPL84 was shown to fully restore *CFTR* function in Human Nasal Epithelial (HNE) and Human Bronchial Epithelial (HBE) cells derived from CF patients carrying the 3849 + 10 kb C->T variant [14]. SPL84 lung biodistribution studies in mice and monkeys showed that SPL84 was properly distributed in the lungs and was detected in all the respiratory epithelium, including within the nucleus [15]. A full battery of safety pharmacology and toxicological studies was completed with SPL84, with no alarming safety findings. SPL84 was shown to be specific to the SPL84 allele, showed no full homology with any other human gene sequences and did not influence candidate off-target genes in-vitro with partial homology. The toxicity of SPL84 was tested following weekly inhalation in 4-week and 9-week toxicological studies in mice and monkeys. No SPL84-related clinical signs were observed in these studies, nor any effect on body weight, food consumption, or clinical pathology. All the microscopic changes in the lungs were regarded as non-adverse and reflected a normal clearance process for inhaled material and/or uptake into resident macrophages in the airspace and local lymph nodes. Systemic exposure in both species was low, as anticipated for an inhaled ASO. SPL84 showed no genotoxic effect [16]. In this phase 1 study, the safety, tolerability, and pharmacokinetics (PK) of a single inhaled dose of SPL48 was evaluated in HVs.

2. Methods

This study was conducted in accordance with Israel ethical principles derived from the Declaration of Helsinki, council for international organizations of medical sciences (CIOMS), and Good Clinical Practices (GCP). The study was approved by the Israel Ministry of Health and Institutional Review Board (IRB) of Hadassah University Medical Center, Jerusalem, Israel (MOH_2022–12–28_012201). Following a detailed explanation all subjects signed a written consent form.

2.1. Study design

The study was a phase 1, randomized, double-blind, placebo-controlled, single dose study in HV aimed to evaluate the safety, tolerability and PK of SPL84 administered by inhalation using an approved device (Aerogen [formerly Philips] InnoSpire Go). On the morning of

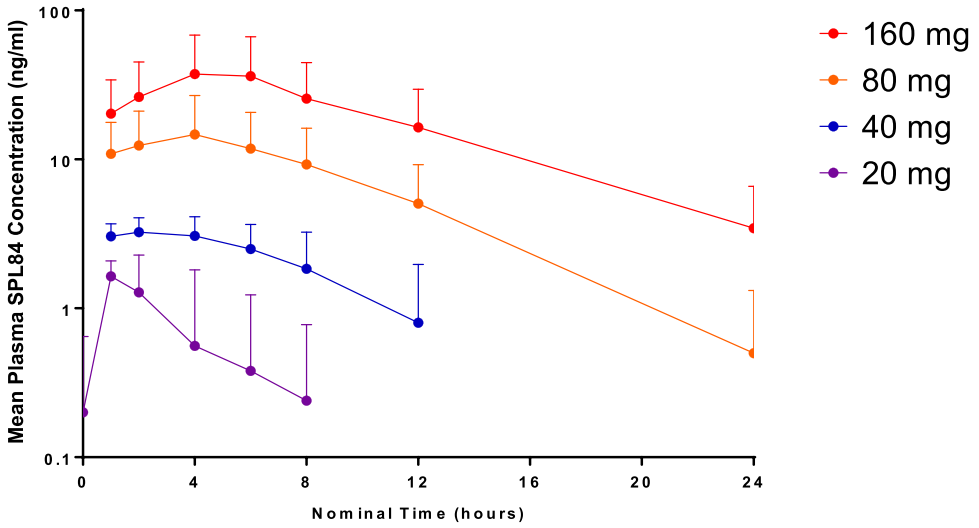

Fig. 2. Plasma SPL84 PK Profile Following Inhalation Administration of Nebulized SPL84 Solution.

Day 1, eligible, enrolled subjects received a single dose of study intervention by inhalation according to their assigned cohort and randomization. Blood samples were obtained periodically for 24 h for the evaluation of SPL84 plasma concentration. Safety was evaluated by repeated performance of pulmonary function tests, and 12-leads ECG recording. Subjects were discharged from the Phase 1 unit on Day 2, 24 h post-dose, The subjects returned to the Phase 1 unit on Day 3 and 4 (for collection of blood samples for PK at 48- and 72-hours post-dose, respectively). Subjects were followed daily by phone interview (Days 5–6) and returned to the clinic on Day 7 and Day 31/end of study visit for follow-up safety assessments (Fig. 2).

There were 4 dose cohorts in the study: 20, 40, 80, and 160 mg (Supp Fig. 1). For each cohort, 8 subjects were randomized on Day 1 in a 3:1 ratio to active (SPL84): control (matched placebo; 0.9% saline). Dosing was done in a staggered manner; in each cohort, initially 2 sentinel subjects (1 active and 1 placebo) were randomized and dosed. Twenty-four hours later, if no safety signal were detected the remaining 6 subjects of the same cohort were randomized and dosed (5 active and 1 placebo).

The decision to escalate to the next dose level was made based on the recommendation of an independent study steering committee (SSC), which reviewed blinded emerging safety and tolerability data of subjects in each cohort. A minimum of 6 days post-dose safety data was reviewed by the SSC to determine the next dose level. All accumulated safety data of the study was reviewed at the end of the study by the SSC before giving approval to continue to Phase 2.

The main inclusion criteria were healthy male adults, 18 to 50 years old with Body Mass Index (BMI) 19.0–30.0 kg/m2, inclusive, and who had no difficulties in receiving drugs by inhalation, as tested at screening. Main exclusion criteria were recent diagnosis of lung disease, including chronic respiratory disease, abnormal FEV1 at screening (FEV1 $<$80% predicted or FEF25–75 $<$ 70% predicted at screening). and oxygen saturation $\leq$95% at screening. Supp. Figure 2 describes the disposition of subjects in the study.

2.2. SPL84 drug substance and product

SPL84 Drug Substance (DS) is a uniformly modified 2′-O-MOE (2-O-(2-methoxyethyl)) phosphorothioate ASO composed of 19 nucleotide bases, in the form of a sodium salt. SPL84 Drug Product (DP) is manufactured at a concentration of 20 mg/mL and formulated in 0.9% saline. SPL84 The unblinded pharmacist prepared and/or diluted the 20 mg/ml DP using the placebo to achieve the different dose strengths while the volume of SPL84 in the nebulizer remained constant (0.9% saline).

2.3. SPL84 delivery device

SPL84 DP or Placebo were delivered by oral inhalation using the Aerogen (formerly Philips) InnoSpire Go (ISG) handheld vibrating mesh nebulizer through the device mouthpiece without additional accessories. The nebulizer in combination with SPL84 had the following main attributes: using a nominal fill volume of 5 mL of SPL84 DP or Placebo, the residual volume left in the nebulizer following nebulization is ~ 12.5% of nominal dose and the average nebulization time is ~ 8 min.

2.4. Study outcomes

The primary objective of the study was to evaluate the safety and tolerability of single ascending doses of SPL84 administered by inhalation and identify the Maximum Tolerated Dose (MTD) in healthy volunteers, by evaluating the incidence, nature, and severity of AEs, and SAEs; and evaluating changes from baseline in vital signs, clinical laboratory values, ECG, physical examination, and pulmonary function (forced expiratory volume in 1 second [FEV1], forced vital capacity [FVC], and forced mid-expiratory flow [FEF25–75]).

Spirometry (pulmonary function testing) was performed locally using the MIR Spirolab spirometer per American Thoracic Society (ATS)/European respiratory society (ERS) Standards. Global lung function initiative (GLI) reference equations were used to calculate the percent predicted values. The following parameters were evaluated:

- FEV1 - volume exhaled in 1 second
- FVC - the amount of air that can be forcibly exhaled from the lungs
- FEF25–75 - exhaled vital capacity at 25 and 75% of the pulmonary volume

Each test (flow-volume loop) was reviewed by the investigator and medical monitor (MM), with input from one of the members of the SSC (clinical pulmonologist) when needed.

The investigator was obligated to assess the relationship between study intervention and each occurrence of each AE/SAE and determine if it was related or not related. The investigator used clinical judgment to determine the relationship. AEs in the study were to be treated with appropriate therapies. A Grade 4 (as defined by national cancer institute [NCI] CTCAE Version 5) adverse reaction required permanent discontinuation of study intervention. If Grade 3 toxicity was noted during the dose administration, the administration was to be halted and the subject assessed. If the adverse reaction symptoms resolved promptly, then study intervention administration could be re-initiated. Any Grade $\geq$ 3

Table 1
Arithmetic Mean (Arithmetic SD) of Plasma SPL84 Pharmacokinetic Parameters Following Inhalation Administration of Nebulized SPL84 Solution.

PK Parameter	A1 (20 mg)		A2 (40 mg)		A3 (80 mg)		A4 (160 mg)	
	Arithmetic Mean (Arithmetic SD)	N	Arithmetic Mean (Arithmetic SD)	N	Arithmetic Mean (Arithmetic SD)	N	Arithmetic Mean (Arithmetic SD)	N
C_{max} (ng/mL)	1.78 (0.672)	5	3.34 (0.783)	5	14.7 (12.0)	6	38.9 (31.4)	6
T_{max}* (hr)	1.22 (1.20,2.22)	5	2.18 (1.20,4.20)	5	4.18 (2.20,4.20)	6	4.22 (4.18,6.18)	6
T_{last}* (hr)	2.22 (1.22,8.38)	5	8.18 (6.35,12.20)	5	12.75 (12.18,24.18)	6	24.19 (24.18,24.25)	6
AUC_{0-t} (hr*ng/mL)	10.2 (NC)	2	24.8 (12.5)	5	138 (117)	6	416 (327)	6
AUC_{inf} (hr*ng/mL)	NC (NC)	0	NC (NC)	0	205 (156)	3	444 (353)	6
AUC% extrap (%)	NC (NC)	0	NC (NC)	0	4.95 (2.28)	3	5.81 (2.78)	6
AUC_{0-6} (hr*ng/mL)	NC (NC)	1	16.2 (4.65)	5	69.3 (51.5)	6	165 (127)	6
AUC_{0-8} (hr*ng/mL)	NC (NC)	1	23.3 (4.12)	4	90.7 (67.4)	6	228 (178)	6
AUC_{0-24} (hr*ng/mL)	NC (NC)	0	NC (NC)	0	198 (150)	3	415 (327)	6
$t_{1/2}$ (hr)	NC (NC)	0	NC (NC)	0	3.90 (1.16)	3	5.30 (0.968)	6
CL/F (L/hr)	NC (NC)	0	NC (NC)	0	234 (213)	3	188 (99.6)	6
Vz/F (L)	NC (NC)	0	NC (NC)	0	1080 (636)	3	1400 (775)	6

* = PK Parameter Reported as median (minimum, maximum) | NC = Not Calculated.

adverse reactions suspected of being related to study intervention was to result in study intervention discontinuation.

2.5. SPL84 plasma concentration analysis

The secondary objective of the study was to characterize the pharmacokinetic (PK) of SPL84 administered by inhalation in healthy volunteers based on measuring the SPL84 concentration in plasma. Plasma samples were collected at multiple timepoints over 72 h following study drug administration, as well as 7- and 31-days post-dose. Samples were analyzed for SPL84 drug concentrations using a validated Anion-Exchange High-Performance Liquid Chromatography method. The lower limit of quantitation (LLOQ) was 1 ng/mL.

The method was validated in compliance with the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192,217/2009) and in general compliance with the US FDA Guidance for Industry for Bioanalytical Method Validation (May 2018). Quantification was performed based on an external calibration curve generated from a standard dilution series in human plasma. In the first step of the assay, human plasma lysates were prepared by Proteinase K treatment. Then, the parent compound was hybridized with the PNA and was subsequently analyzed by AEX-HPLC coupled to a fluorescence detector. Linear calibration curves (weighted 1/X) were calculated from 1.0 ng/mL to 2000.0 ng/mL in human plasma.

2.6. Pharmacokinetic analysis

PK parameters were determined, where possible, using non-compartmental methods performed using Phoenix WinNonlin, version 8.3 or higher, according to the PK Analysis Plan. In brief, C_{max} and T_{max} were determined by direct observation of the plasma concentration-time curve.

The terminal elimination half-life ($t_{1/2}$) was estimated by non-linear regression analysis of the terminal elimination slope, if feasible:

$t_{1/2} = \frac{\ln 2}{\lambda_z}$ The area under the curve to the final sample with a concentration greater than lower limit of quantification (AUC0-t) was calculated using the linear trapezoidal method. Area under the curve to infinity (AUC_{inf}) was calculated based on the last observed concentration Clast(obs), calculated using the linear up log down rule, if feasible:

$$AUC_{inf} = AUC_{0-t} + \frac{C_{last(obs)}}{\lambda z}$$

Where $C_{last(obs)}$ was the last observed quantifiable concentration.

At least 3 consecutive measurable concentrations were required to determine AUCs. AUCinf were reported when the area was determined by extrapolation is <20%. Parameters further calculated using AUCinf, such as clearance and volume of distribution, were handled the same way as AUCinf.

2.7. Statistical analysis

Due to its exploratory nature, the analyses for this study were mainly descriptive. Data analysis was based on descriptive statistics for the dose groups, and when appropriate, pooled across dose groups. For continuous variables, the statistics include the following: geometric mean, mean, median, log-scale standard deviation, standard error of the mean, minimum and maximum. For categorical variables the statistics include frequency and proportions. All analyses were performed as outlined in the Statistical Analysis Plan.

3. Results

3.1. Drug concentration and pharmacokinetics

Following the administration of an inhaled nebulized solution of SPL84, plasma concentrations of SPL84 rapidly appeared in the systemic circulation. The median T_{max} was within a range of 1.22 to 4.22 h, with a tendency for a delayed T_{max} and flatter plasma concentration time profiles at the higher doses. Mean plasma C_{max} and area under the plasma concentration-time curve (AUC0-t) values ranged from 1.78 to 38.9 ng/mL (20 mg to 160 mg) and 10.2 to 416 ng.hr/mL (20 mg to 160 mg), respectively. These values are relatively low compared to the total dose inhaled, as expected for an inhaled drug. The increase in plasma SPL84 exposure following escalating doses was higher than expected deviating from dose proportionality. For example, Cmax for 160 mg was 11.6- and 2.6-fold higher than the values for 40 mg and 80 mg, with similar ratios for AUC0-t. Inter-individual variability of Cmax and AUC0-t was high (>80%) for the 80 and 160 mg cohorts. Following Cmax, plasma concentrations rapidly declined with an elimination half-life (t1/2) of 3.9 and 5.3 hrs for the 80 and 160 mg cohorts, respectively. The low concentration noted following 20 mg and 40 mg administration did not allow us to calculate the elimination rate constant for these cohorts.

The $AUC_{0\rightarrow\infty}$ and C_{max} of SPL84 following the highest dose (160 mg) were 17 and 56-fold lower respectively as compared to the exposure following administration of the dose that defined the NOAEL (48 mg/kg) in the 9 weeks GLP mice study.

A summary of the PK parameters in the study are presented in Table 1 and in Fig. 2.

3.2. Safety evaluation

The administration of a single nose of inhaled SPL84 was safe and well tolerated, with no significant changes from baseline in vital signs,

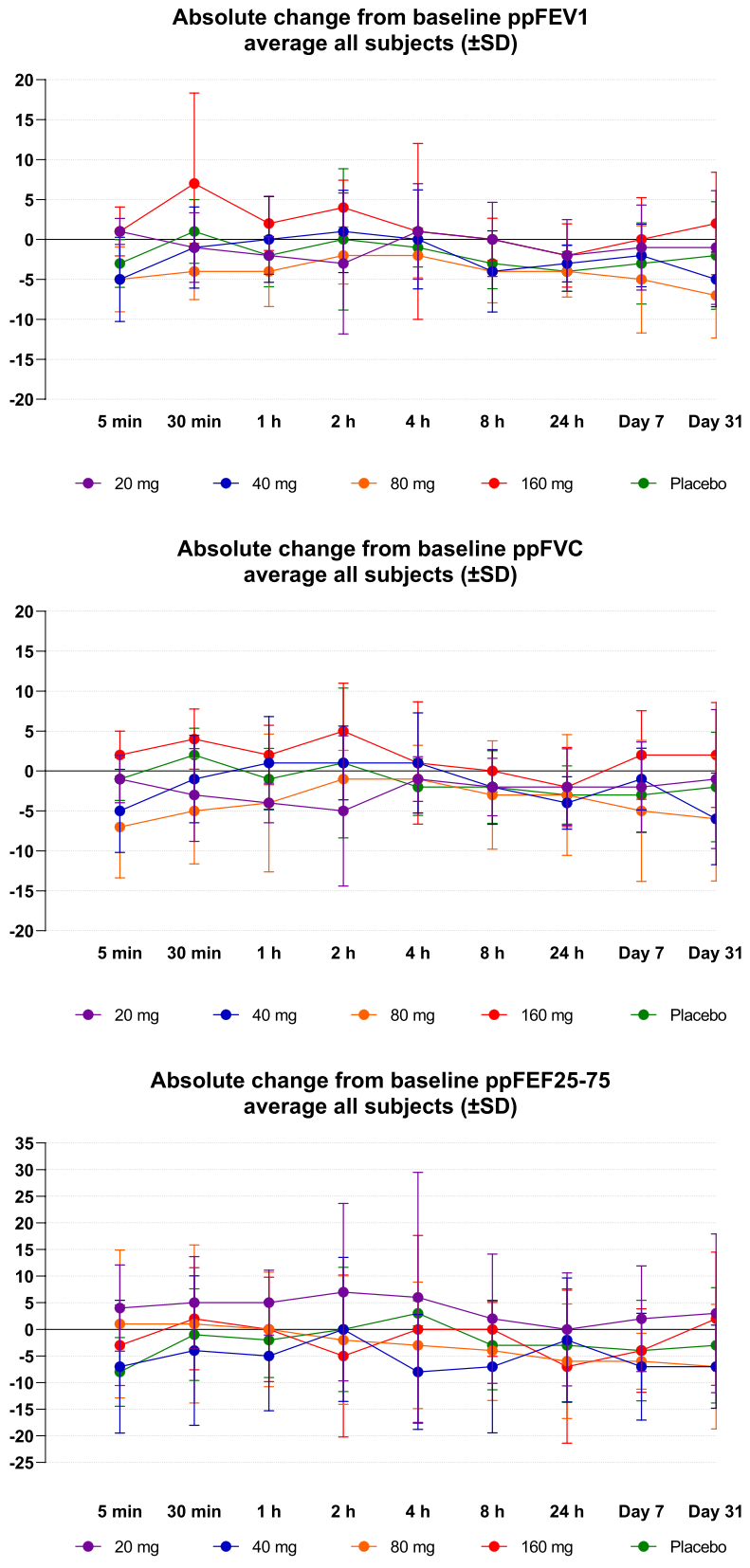

Fig. 3. Mean Absolute Change from Baseline (±SD) in Percent Predicted Spirometry Values Per Cohort and Per Treatment Arm.

clinical laboratory values, ECG, physical examination, or pulmonary function. Overall, there were no clinically significant adverse events, and all were given an NCI CTCAE grade of mild, except for one AE which received a grade of moderate (paronychia, not related).. There were 19 AEs reported during the study; 3 of these AEs were reported by subjects who received placebo (cough, cold, headache). These 19 AEs were reported by 11 subjects (a few subjects experienced numerous AEs that were part of the same event). All but 2 of the AEs were assessed by the

investigator as not related to the study drug (Supp Table 1).

There was no significant or irreversible effect on pulmonary function. It was recommended by the expert pulmonologists in the SSC that a decrease in spirometry values of more than 15 percent predicted FEV1 or FVC and 25 percent predicted FEF25–75 be considered as an AE, as this may be considered a significant decrease and not just normal within-subject variation [17]. Two subjects (one in the 80 mg and one in the 160 mg cohort) experienced a decrease in FEF25–75 (of ~20% and ~30%, respectively) which were considered by the investigators to be an AE, however the decreases were asymptomatic, transient, and did not require any medical intervention. The average absolute change from baseline in percent predicted FEV1, FVC, and FEF25–75 for each cohort and placebo is presented in Fig. 3. Overall, the change in measurements were within normal range.

4. Discussion

The primary objective of this study was to evaluate the safety and tolerability of a single inhaled dose of SPL84 in HVs. There were no SAEs in the study, and there were no clinically significant adverse events. Overall, SPL84 was safe and well tolerated, with no safety concerns, and importantly, no significant effect on pulmonary function. All AEs were mild, except for one non-SPL84 related AE which was moderate, and all but 2 of the AEs were not related to the study drug. The 2 AEs which were determined to be related to the study drug were both mild decreases in percent predicted FEF25–75 (as compared to baseline). These AEs were transient, mild, and asymptomatic, and resolved without any medical intervention. None of the AEs recurred during the 30-day follow-up period. Additionally, FEF25–75, which is a sensitive measurement that represents function of the small airways, is a very variable measurement, and the decreases may reflect normal within-subject variation [17]. Furthermore, for the healthy volunteers in the study, who were not previously familiar with spirometry tests, the large number of spirometry tests often led to fatigue, which may have caused a subtle decrease in the test results.

In conclusion, SPL84 was shown to be safe and well-tolerated when administered to HVs as a single inhaled dose up to 160 mg, with minimal systemic exposure. The successful completion of the study enabled the initiation of a multi-dosing of SPL84 in people with CF carrying the 3849 + 10 kb C->T *CFTR* variant in a Phase 2 study.

Declaration of competing interest

The following authors are SpliSense company employees: Lital Friedman, Asaf Cohen, and Gili Hart. Prof. Kerem serves as an external medical consultant to SpliSense and is the spouse of the scientific founder and Chief Scientific Officer of SpliSense.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2024.10.004.

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