A Phase 1b Study of Zotatifin for the Treatment of Mild to Moderate COVID (PROPEL)

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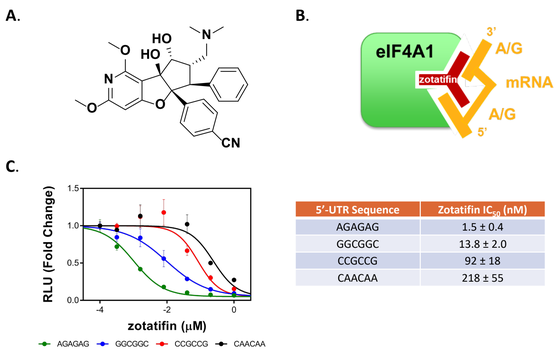
Background

- **Zotatifin (eFT226) is a potent and selective inhibitor of eukaryotic initiation factor 4A (eIF4A), a host ribonucleic acid (RNA) helicase required for SARS-CoV-2 replication**
- **Zotatifin was developed using a ligand-based design strategy[1] based on the flavagline class of natural products (e.g., silvestrol and rocaglamide A) which have broad spectrum activity against a variety of RNA viruses including coronaviruses, picornaviruses, Ebola, etc.**
- **Zotatifin selectively inhibits translation of RNA containing specific short polypurine motifs in their extended 5′- untranslated region (5′-UTR)[1]**
- **Two such highly conserved motifs are found in the SARS-CoV-2 extended 5′-UTR[2]**
- **These nonclinical data provided the rationale to evaluate the safety, efficacy and pharmacokinetics of zotatifin in adult patients with mild or moderate COVID-19**

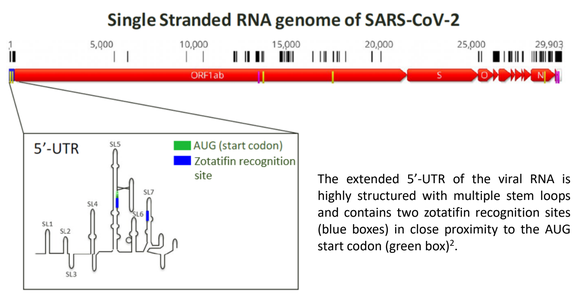
Figure 1. Zotatifin Is a Sequence-Specific Translational Repressor



5′-UTR Sequence	Zotatifin IC_{50} (nM)
AGAGAG	1.5 ± 0.4
GGCGGC	13.8 ± 2.0
CCGCCG	92 ± 18
CAACAA	218 ± 55

A) Chemical structure of zotatifin. **B**) Schematic of the ternary complex interactions [eIF4A-zotatifin-mRNA]. **C**) Luciferase reporter gene constructs containing 5′-UTRs with 6-mer sequence motif repeats were transiently transfected into the MDA-MB-231 cell line and treated with increasing concentrations of zotatifin for 4 hr.

Figure 2. Zotatifin Recognition Sites in the SARS-CoV-2 RNA



The extended 5′-UTR of the viral RNA is highly structured with multiple stem loops and contains two zotatifin recognition sites (blue boxes) in close proximity to the AUG start codon (green box)[2].

Objectives

Primary Objective

- To evaluate the safety and tolerability of zotatifin administered intravenously (IV) or subcutaneously (SQ) to adults with mild or moderate COVID-19

Secondary Objectives

- To evaluate the antiviral activity of zotatifin in adults with mild or moderate COVID-19
- To evaluate the plasma pharmacokinetics (PK) of zotatifin administered IV or SQ

Exploratory Objectives

- To assess antiviral activity using saliva specimens, virus resistance, circulating inflammatory or coagulopathy markers, and other indicators of disease worsening, after zotatifin administration in adults with mild or moderate COVID-19

Methods

Study design and treatment

- Randomized, double-blind, placebo-controlled, dose-escalation trial
- 36 patients randomized 3:1 zotatifin or placebo in 3 cohorts of 12 patients
- Three zotatifin dose levels: 0.01, 0.02, or 0.035 mg/kg
- IV administration of zotatifin in first two patients in Cohort 1 (1 active and 1 placebo), all subsequent trial patients dosed SQ

Patient eligibility - key inclusion criteria

- Outpatient adults < 65 yrs old with mild/moderate COVID-19 (≥ 1 symptoms at randomization), without significant cardiorespiratory disease, or renal or hepatic impairment, BMI < 35 kg/m2
- Positive for SARS-CoV-2 RT-PCR or antigen from oral or nasal sample collected ≤7 days of randomization

Assessments

- Adverse events (AEs)/serious adverse events (SAEs), safety laboratory tests and objective tests measured Day 1-28
- Virology: nasal swabs Days 1, 4, 8, and 15 and saliva measured Day 1-15
- WHO-9 clinical improvement ordinal scale score measure Day 1-15
- Pharmacokinetic samples were scheduled for collection at 15 and 30 minutes, and 1, 2, 3, 6, 72, 168, 216, and 336 hours post-dose

Analyses

- Viral load (log10 copies/mL) was determined by qRT-PCR and changes from baseline were summarized on scheduled visit days (Days 1, 4, 8, 10, & 15) for nasal swabs and on daily collections for saliva specimens; cohorts were combined for data analysis
- Time to first viral load undetectability (VLU) within the 15-day observation period was determined using all scheduled and unscheduled collections for both nasal swabs and saliva samples except in patients where 1st day VL < limit of detection (LOD), which were excluded from the analysis; cohorts were combined for data analysis; Log-rank test and hazard ratio (95% CI) from the Cox proportional hazards model are provided
- Using plasma concentration-time profiles, individual PK parameters for each patient were determined by noncompartmental analysis (NCA) and summary statistics subsequently were assessed at each dose level
- All analyses are based on preliminary data as of 2/06/2023 prior to database lock

Results

Table 1. Patient Demographic and Baseline Characteristics

Characteristic		Cohort 1 0.01 mg/kg (n=9)	Cohort 2 0.02 mg/kg (n=9)	Cohort 3 0.035 mg/kg (n=9)	Pooled Placebo (n=9)
Age, median (range), years		39 (22-59)	44 (28-58)	47 (25-60)	48 (21-63)
Gender	• Male	5	1	1	4
	• Female	4	8	8	5
Race	• White	8	7	7	7
	• Black or African descent	0	2	2	1
	• Other	1	0	0	1
Body Mass Index, median (kg/m^2)		27	28	28	29

Table 2. Treatment Emergent Adverse Events in > 1 Subject for Zotatifin-Treated Subjects in Cohorts 1, 2, 3, and Pooled Placebo Subjects

MedDRA term	N (%)							
	Cohort 1 (n=9)		Cohort 2 (n=9)		Cohort 3 (n=9)		Pooled Placebo (n=9)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Injection site reactions*	5 (56%)	0 (%)	8 (89%)	0 (%)	6 (67%)	0 (%)	0 (%)	0 (%)
Diarrhea	2 (22%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	2 (22%)	0 (%)
Hematocrit decreased	2 (22%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)
Headache	2 (22%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)

*Includes all injection site reactions of erythema, swelling, pain, pruritis, and warmth

- One grade 3 AE of CPK elevation in zotatifin portion of Cohort 1, no grade ≥ 3 AEs in Cohorts 2, 3, or placebo
- No serious adverse events

Results (cont'd)

Figure 3. Viral Load Kinetics: Absolute Change From Baseline Over Time (Mean ± SEM) In Combined Cohorts

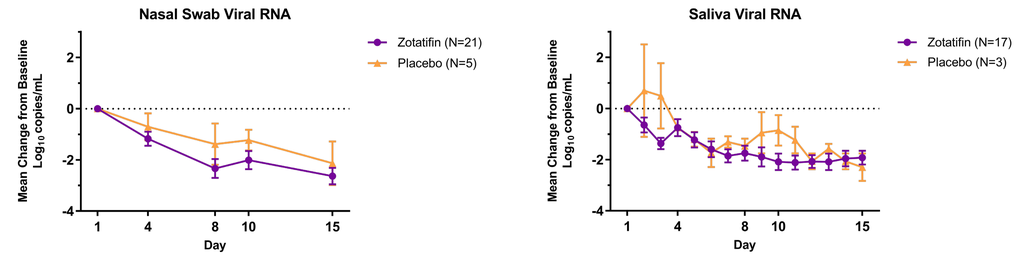
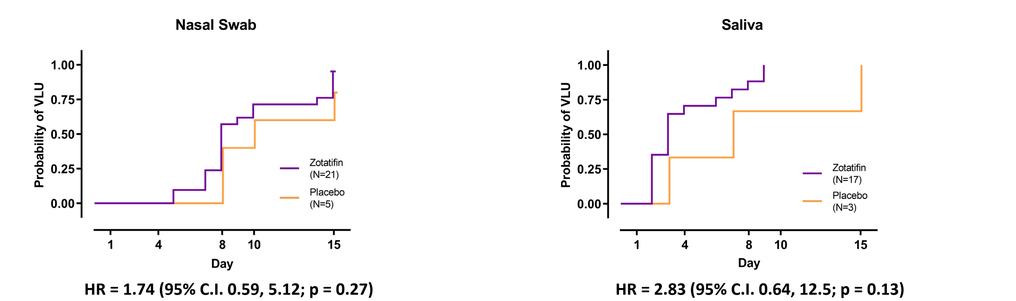


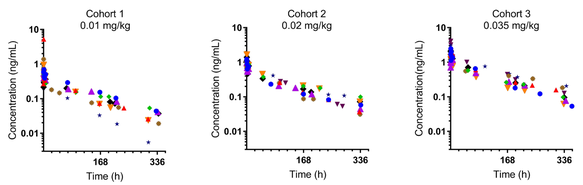
Figure 4. Time to First Viral Load Undetectability (VLU) In Combined Cohorts



HR = 1.74 (95% C.I. 0.59, 5.12; p = 0.27)
Median time to VLU (days) = 8 (zotatifin) vs 10 (placebo)

HR = 2.83 (95% C.I. 0.64, 12.5; p = 0.13)
Median time to VLU (days) = 3 (zotatifin) vs 7 (placebo)

Figure 5. PK Parameters From Subcutaneous Zotatifin



NCA Parameter	0.01 mg/kg (N=8)	0.02 mg/kg (N=9)	0.035 mg/kg (N=9)
AUC_{inf} (h.ng/mL)	45.4 (31.6)	85.4 (18.5)	159 (26.5)
C_{max} (ng/mL)	0.68 (43.8)	1.2 (18.7)	1.9 (43.7)
Cl (mL/min/kg)	3.66 (31.4)	3.89 (18.5)	3.66 (26.5)
Vss (L/kg)	28.2 (24.3)	32.8 (21.5)	32.5 (21.6)
T_{max}(h)	0.52 (0.33,1.0)	0.30 (0.28,0.52)	0.30 (0.28,3.2)
$T_{1/2}$ (h)	98 (82,125)	97 (82,141)	103 (92,126)

AUC_{inf}: Area under the curve from time zero to infinity; C_{max}: Maximum plasma concentration; V_{ss}: Volume of distribution at steady-state; Cl plasma clearance; T_{max}: time of C_{max}; $T_{1/2}$: Elimination half-life; For AUC_{inf} / C_{max} / V_{ss} / Cl: Geomean (Geomean CV%) shown; For T_{max} & $T_{1/2}$: Median (IQR) shown; CV: coefficient of variation; IQR: interquartile range

- The first patient in Cohort 1 received two 0.01 mg/kg IV doses of zotatifin, administered 6 days apart. PK concentrations and parameters for this patient (not shown) were consistent with expectations for the doses administered.
- The concentration-time profile of zotatifin (Cohorts 1-3) following SC administration was similar to that reported previously following IV administration[3], demonstrating a terminal elimination half-life ($t_{1/2}$) of ~ 4 days, high steady-state volume of distribution (V_{ss}) of 31 L/kg, low plasma clearance (Cl) of 3.7 mL/min/kg, and excellent PK linearity over the evaluated dose range.

Summary

- **Zotatifin was safe, well tolerated and demonstrated a trend in clinical antiviral activity in patients with mild to moderate COVID-19 which supports further clinical development**
- **The administration of zotatifin as a single subcutaneous injection supports a *point of care* treatment for COVID-19**

Acknowledgements

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References

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