EudraCT TFF-V2-001 study results update: June 30th, 2025

The TFF-V2-001 study was terminated early due to poor enrollment.

EudraCT number: 2021-006633-19

Protocol TFF-V2-001 study title: A Phase 2, Open-Label, Randomized, Safety, Pharmacokinetic, and Efficacy Study of Voriconazole Inhalation Powder Compared to Oral Voriconazole Tablets in Subjects with Acute Invasive Pulmonary Aspergillosis (IPA)

Primary endpoints: The primary endpoint of the TFF-V2-001 study was safety and tolerability as assessed by the following:

- Incidence and severity of treatment emergent adverse events (TEAEs).
- Incidence of TEAEs leading to study discontinuation.
- Incidence of TEAEs leading to death (all-cause mortality) during the study.
- Incidence and severity of study drug-related TEAEs.

Patient population: Patients with acute invasive pulmonary aspergillosis

- Enrollment goal: 40 patients
- Actual enrollment: 5 patients

PROTOCOL SYNOPSIS

Name of Sponsor/Company: TFF Pharmaceuticals, Inc.

Name of Investigational Product: Voriconazole Inhalation Powder

Name of Active Ingredient: Voriconazole in Voriconazole Inhalation Powder

Protocol Number: TFF-V2-001

Phase: 2

Title of Study: A Phase 2, Open -Label, Randomized, Safety, Pharmacokinetic, and Efficacy Study of Voriconazole Inhalation Powder Compared to Oral Voriconazole Tablets in Subjects with Acute Invasive Pulmonary Aspergillosis (IPA)

Objectives:

Primary:

Primary Objective

The primary objective of this study is to compare the safety and tolerability of 80 mg of Voriconazole Inhalation Powder twice daily (BID) in subjects with acute IPA to the safety and tolerability of BID oral voriconazole tablets administered per standard of care (SOC) after a 13--week treatment period.

Primary Endpoint

The primary endpoint is safety and tolerability as assessed by the following:

- Incidence and severity of treatment emergent adverse events (TEAEs).
- Incidence of TEAEs leading to study discontinuation.
- Incidence of TEAEs leading to death (all-cause mortality) during the study.
- Incidence and severity of study drug-related TEAEs.

Secondary:

Secondary Objectives

The secondary objectives are as follows:

- To evaluate voriconazole plasma exposure of multi-dose inhalation of Voriconazole Inhalation Powder versus oral voriconazole tablets.
- To compare 80 mg BID of Voriconazole Inhalation Powder to SOC oral voriconazole tablets in treating acute IPA for up to 13 weeks.
- To evaluate the clinical cure of IPA in subjects treated with 80 mg of Voriconazole Inhalation Powder compared to SOC oral voriconazole tablets.

Secondary Endpoints

The secondary endpoints are as follows:

- Voriconazole plasma concentration at specified timepoints.
- When possible, for evaluable subjects when a series of samples has been collected, voriconazole plasma pharmacokinetic (PK) parameters; time to reach

maximum observed concentration (T_{max}), maximum observed concentration (C_{max}), area under the concentration-time curve, from time 0 to the last observed non-zero concentration (AUC_{last}), area under the concentration-time curve, from time 0 to the 12-hour time point (AUC_{0-12h}), area under the concentration-time curve, from time 0 extrapolated to infinity (AUC_{inf}), half-life, mean residence time (MRT_{last}), apparent volume of distribution during terminal phase (Vz/F), apparent total plasma clearance after oral administration (Cl/F) and other parameters considered appropriate, such as a comparison of systemic exposure between oral and inhaled routes.

- Radiologic response as evidenced by improvement in lesion size and/or lesion number.
- Clinical response as evidenced by improvement in the sign and symptom severity score using a 5-point severity scale adapted from the Common Terminology Criteria for Adverse Events.
- Mycologic response as evidence by clearance of Aspergillus infection.
- Change in plasma, serum, or bronchoalveolar lavage (BAL) galactomannan (GM) antigen at 8 and 13 weeks.

Exploratory:

Exploratory Objectives

The exploratory objectives are as follows:

- To compare all-cause mortality between the Voriconazole Inhalation Powder and oral voriconazole tablets groups through 17-weeks.
- To compare the number of IPA-related hospital admissions following treatment with Voriconazole Inhalation Powder and oral voriconazole tablets over 13 weeks.
- To compare the number of IPA-related mortality following treatment with Voriconazole Inhalation Powder and oral voriconazole tablets over 17 weeks.
- To characterize the exposure concentration of voriconazole in BAL (when collected) of multi-dose inhalation of Voriconazole Inhalation Powder versus oral voriconazole tablets at any timepoints when collected and comparison to blood levels collected at a matching time point. Note: If BAL collected, a corresponding PK blood draw (unscheduled timepoint if necessary) should be drawn.
- To characterize the dose changes of concomitant medications and characterize systemic concentrations of select concomitant medications.
- To compare the level of secondary fungal infections in subjects infected with acute IPA after being treated with Voriconazole Inhalation Powder compared to oral voriconazole tablets for 13 weeks.
- Compare discontinuations in the Inhaled Voriconazole Powder arm with discontinuations in the oral voriconazole arm.

Exploratory Endpoints

The exploratory endpoints are as follows:

- All-cause mortality occurring through 17 weeks (death from any cause).
- IPA-related hospitalization during the treatment period.
- Mortality related to IPA fungal infection through 17 weeks.
- Bronchoalveolar lavage levels of voriconazole at specified timepoints; BAL to plasma ratios of voriconazole.
- Frequency and magnitude of dose adjustments of calcineurin inhibitors medications.
- Frequency and magnitude of dose adjustments of oral voriconazole.
- Addition of anti-fungal medications to control yeast infections.
- Discontinuations due to secondary fungal infections requiring treatment, such as candidiasis, during the 13-week treatment period.
- Compare the number of subjects who discontinue the oral arm and choose to receive Voriconazole Inhalation Powder to the number of subjects who discontinue the inhaled arm and subsequently receive SOC.

Study Design:

This is an open-label, randomized, comparator-controlled, parallel, safety, PK and efficacy study evaluating 80 mg Voriconazole Inhalation Powder BID (160 mg total daily dose) compared to oral voriconazole tablets BID dosed per physician standard practice in adult subjects with acute IPA. The oral voriconazole tablets SOC dose will start at 200 mg BID (400 mg total daily dose) and may be adjusted to achieve a therapeutic drug monitoring level between 1.0 and 5.5 µg/mL (100 to 300 mg per dose) inclusive.

Methodology:

Subjects may be screened upon hospitalization for proven, probable, or possible IPA infection. Subjects will be randomized 3:1 to receive either Voriconazole Inhalation Powder (80 mg) or oral voriconazole tablets BID (200 mg). Subjects will receive study treatment BID for up to 13 weeks.

Subjects presenting with acute IPA may participate as in-patient or out-patient (upon qualification). Subjects will be screened for eligibility up to 2 weeks prior to randomization. If qualified, subjects will be randomized 3:1 to 1 of 2 treatment arms to receive BID treatment for 13 weeks. Subjects randomized to the oral voriconazole tablets arm may be dose adjusted during the study at specified timepoints to maintain a therapeutic drug monitoring level between 1.0 and 5.5 µg/mL inclusive. Following 13 weeks of BID treatment, subjects will return to the clinic 17 weeks following their first dose for follow up safety assessments.

Subjects in the oral voriconazole arm who choose to withdraw from the study or discontinue treatment for any reason will be given the option to receive Voriconazole Inhalation Powder after consultation with the Sponsor Medical Monitor. Subjects who choose to receive Voriconazole Inhalation Powder will be required to remain in the study and follow the schedule of assessments starting on Day 1. They will be treated with Voriconazole Inhalation Powder for 13 weeks.

Sample Size Justification:

A total of up to 40 adult male and female subjects with an acute IPA infection will be enrolled into the study; 30 subjects will be randomly assigned to Voriconazole Inhalation Powder arm and 10 subjects will be randomly assigned to the oral voriconazole arm.

This study is not powered for hypothesis testing. The sample size has been selected to provide an adequate number of subjects to evaluate safety and PK.

Ongoing Safety Monitoring:

An independent Data Safety Monitoring Board (DSMB) will monitor the safety and tolerability of voriconazole in this study. The DSMB will undertake ongoing review of safety data, including but not limited to review of laboratory data, adverse events of special interest, serious adverse events and reasons for subject discontinuation. The DSMB will meet as outlined in the DSMB charter. Enrollment will continue during all DSMB reviews unless the DSMB recommends terminating the study for safety concerns.

Number of Subjects (Planned): Up to a total of 40 adult male and female subjects with an acute IPA infection will be enrolled. Thirty subjects will be randomly assigned to receive Voriconazole Inhalation Powder, and 10 subjects will be randomly assigned to receive oral voriconazole. Randomization will be stratified based on the subject's baseline medical condition (e.g., solid organ transplant or hematological malignancy) at the time of randomization.

Diagnosis and Main Criteria for Inclusion:

Inclusion criteria

Subjects meeting the following inclusion criteria may be enrolled into the study:

1. Male or non-pregnant, non-lactating female aged 18 years or older at screening.
2. Diagnosed with acute proven or probable IPA prior to randomization per the adapted Idem EORTC/MSG criteria (Blot et al, 2012; Donnelly et al, 2020; Hałaburda-Rola et al, 2021). Lung transplant recipients may also be diagnosed per the International Society of Heart Lung Transplant (ISHLT) consensus statement (Husain et al, 2011).

   Note:

Real-life criteria used in the diagnosis of IPA, where applicable in the applied algorithm, are acceptable in consultation with the Sponsor Medical Monitor and include:

- For mycological criteria, galactomannan antigen >0.5 in two consecutive plasma, serum, or BAL fluid samples separated by at least 1 day.
- For radiologic criteria, abnormal classic or non-classic chest CT findings attributable to Aspergillus. Chest X-ray findings obtained per the standard of care can also be used.
- For signs and symptoms, classic or non-classic respiratory symptoms attributable to Aspergillus, for example new or worsening cough, dyspnea, or sputum production.
- Subjects missing either radiologic criteria or compatible signs and symptoms criteria can be enrolled in the study for pre-emptive study treatment of probable IPA. Patients treated pre-emptively must meet the host factor criteria and the mycologic criteria.

Subjects with potential diagnosis of proven or probable IPA may be screened, but the diagnosis of probable or proven IPA must be made before randomization.

Antifungal therapy is permitted prior to randomization if clinically indicated but the duration of antifungal therapy must not exceed 21 days. Antifungal therapy may be started empirically before the subject completes a diagnostic work up if clinically indicated. Only azole antifungals are permitted during the screening period. However, empiric therapy prior to screening may have included antifungals other than azoles as clinically indicated. If patient is treated with an IV azole antifungal during the screening period due to disease severity, the IV antifungal must be weaned to oral at least 2 days prior to randomization.

Antifungal therapy is not permitted prior to randomization in subjects enrolled for pre-emptive study treatment of IPA.

3. Women of childbearing potential (WOCBP) (defined as a woman who has not undergone a hysterectomy or bilateral oophorectomy or has not been naturally postmenopausal for at least 24 consecutive months) must have a negative serum pregnancy test at Screening (Visit 1) and must agree to use highly effective contraceptive methods or abstinence from the time of screening for the duration of time on the study and continue to use acceptable contraceptive methods for 3 months after administration of the last dose of study treatment.

   Male subjects with female partners of childbearing potential must be congenitally sterile or surgically sterile (vasectomy with confirmation of aspermia) or agree to use 2 effective methods of contraception including 1 barrier method (e.g., condom with spermicide and contraception by female partner) for the duration of time on the study and for 3 months after administration of the last dose of study treatment.
4. Subject is considered clinically stable to participate in a 4-month study.

5. Capable of administering inhaled or oral drug product.
6. Subjects taking medications for treatment of other conditions that require or have recommended dose adjustment may be enrolled in the trial but must be willing to be carefully monitored and have medications managed in accordance with the VFEND summary of product characteristics (anticoagulants, benzodiazepines, ciclosporin, efavirenz, ivacaftor, methadone, NSAIDs, opiates, phenytoin, rifabutin, ritonavir, tyrosine kinase inhibitors, tacrolimus, venetoclax).
7. Continuous non-smoker or previous smoker who has not used nicotine-containing products (including vaping) for at least 3 months prior to the first dosing and throughout the study, based on subject's self-reporting at Screening.
8. Body mass index (BMI) ≥ 16.0 and ≤ 32.0 kg/m^2 at screening, and a minimum weight of at least 45.0 kg and a maximum weight of 120 kg at screening.
9. Succeeds in training on the use of the dry powder inhaler and is willing and able to perform adequate inhalation technique in the PI's (or designee's) opinion.
10. Able to generate an inspiratory flow rate of 60 L/minute using the In-Check inspiratory peak flow meter or spirometry.

<u>Exclusion criteria</u>

Subjects meeting any of the following exclusion criteria must not be enrolled into the study:

1. Is legally incapacitated at the time of the screening visit or expected to be so during the conduct of the study in the opinion of the PI or designee.
2. History or presence of uncontrolled clinically significant medical condition or disease that, in the opinion of the PI or designee, would put the safety of the subject at risk, or that could affect the efficacy or safety analysis.
3. Evidence of disseminated systemic aspergillosis or any other systemic fungal diseases.
4. Presence of alcoholism or drug abuse or its history within the past 2 years prior to the first dosing.
5. History or presence of hypersensitivity or idiosyncratic reaction to voriconazole or any triazole antifungal.
6. Has had surgery or any medical condition within 6 months prior to first dosing which may affect the absorption, distribution, metabolism, or excretion (ADME) of the study drug, in the opinion of the PI or designee.
7. Evidence of a mycetoma within the 12 months prior to screening.
8. Evidence of active systemic candidiasis upon screening or randomization.
9. Has active solid tumor cancer requiring chemotherapy and/or radiation therapy during the study. Hematological malignancies that have completed induction chemotherapy and are currently receiving consolidation therapy are allowed.
10. Current suspected or confirmed sepsis.
11. Positive results at screening for tuberculosis, human immunodeficiency virus, hepatitis B surface antigen or hepatitis C virus.

12. Subjects having an ECG with a prolonged QTcF (QT interval corrected according to Fridericia) greater than 450 msec for men and greater than 470 msec for women or has ECG findings deemed abnormal with clinical significance by the PI or designee at screening.
13. Subjects are to be excluded if they are taking medications that are contraindicated in the VFEND summary of product characteristics (astemizole, carbamazepine and long-acting barbiturates, cisapride, ergot alkaloids, everolimus, ivabradine, lurasidone, pimozide, naloxegol, quinidine, rifampicin, sirolomus, St. John's Wort, terfenadine, tolvaptan).
14. Subjects with moderate or severe liver disease as defined by aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5 times the upper limit of normal (ULN) or a total bilirubin level > 3 times the ULN.
15. Subjects who have participated in another clinical study of an investigational drug or device medicine within 1 month before dosing, or participation within 5 half-lives of receiving the last dose of an experimental drug (whichever is longer).

Investigational Product, Dosage and Mode of Administration: The investigational drug will be supplied as capsules for oral inhalation use, each capsule contains 10 mg of Voriconazole. The capsules will be administered using the Plastiape RS00 Model 8 Dry Powder Inhaler device. For each dose (i.e., 8 capsules), multiple inhalations will be required.

Duration of Treatment: Subject participation will last up to 19 weeks (up to 2 weeks screening, 13 weeks treatment, and 4 weeks of follow-up).

Subjects in the oral voriconazole arm who discontinue treatment with oral voriconazole and choose to then receive Voriconazole Inhalation Powder will start the schedule of assessments at Day 1 and spend 13 weeks on treatment with Voriconazole Inhalation Powder and 4 weeks on follow up.

Reference Therapy, Dosage and Mode of Administration: The reference therapy is commercially available oral voriconazole tablets (200 mg and 50 mg).

Criteria for evaluation:

Efficacy:

Assessment of efficacy will include the following endpoints:

- Change in lesion size from baseline to 13 weeks based on radiographic images.
- Change in lesion counts from baseline to 13 weeks based on radiographic images.
- Change in IPA symptoms from baseline to 13 weeks.
- Change in plasma, serum or BAL GM antigen from baseline to 13 weeks.
- Clearance of Aspergillus as assessed by diagnostic mycological criteria.
- IPA-related hospital admissions post initial treatment.

Pharmacokinetics:

Voriconazole plasma and BAL (if collected) PK parameters will be calculated by noncompartmental analysis from available voriconazole concentration time data during the treatment period at specified timepoints.

The following parameters will be calculated:

- AUC_{last}.
- AUC_{0-12}.
- AUC_{inf}.
- C_{max}.
- T_{max}.
- $MRT_{last.}$
- Half-life.
- Cl/F.
- Vz/F (plasma only).
- Other parameters as appropriate.

A summary of selected concomitant medication plasma concentration data (such as tacrolimus) will also be performed.

Safety:

At a minimum, safety will be assessed by the following for up to 30 days following last dose (early terminations) or 17 weeks:

- Number of subjects with TEAEs including all-cause mortality.
- Spirometry.
- 12-lead ECGs.
- Vital sign measurements.
- Number of secondary fungal infections.
- Clinical laboratory tests: biochemistry; hematology, urinalysis.
- Physical examinations.
- Ophthalmologic examinations.

Statistical methods:

Statistical Analyses

A complete description of the statistical analyses and methods will be available in the Statistical Analysis Plan, which will be finalized before the database is locked. All summary statistics will be performed using SAS® statistical software, unless otherwise specified.

All data including, but not limited to, demographics, baseline characteristics, safety assessments, PK parameters, and efficacy assessments will be summarized by

treatment group and where feasible by study visit. No statistical inference testing will be performed.

Summary of TFF-V2-001 key study results:

TFF-V2-001: Demographics, baseline characteristics and treatment duration:

Patient	treatment	age	sex	race	ethnicity	Host factor	Treatment duration total
Patient 1	oral	79	M	W	NHL	Lung Cancer	28 days
Patient 2	oral	45	F	Asian	NHL	Lung transplant	91 days
Patient 3	inhaled	58	F	W	NHL	Lung transplant	91 days
Patient 4	inhaled	51	M	W	NHL	Lung transplant	91 days
Patient 5	inhaled	69	M	W	NHL	Lung transplant	91 days

NHL=Non-Hispanic or Latino

Host factor: medical condition predisposing to invasive pulmonary aspergillosis

TFF-V2-001: Adverse events:

	oral	**inhaled**
	n=2	n=3
Number of TEAEs	12	19
Number of possibly related, probably related or related TEAEs	8	6
Number of patients with possibly related, probably related or related TEAEs	1 (50%)	2 (67%)
Number of patients with related TEAEs	0	0
Number of TEAEs with severity grade 2 or above	8	9
Number of TEAEs with severity grade 3 or above	1	3
Number of possibly related, probably related or related TEAEs with severity grade 2 or above	5	1
Number of possibly related, probably related or related TEAEs with severity grade 3 or above	0	0
Number of TEAEs that occurred in more than 2 patients	0	0
Number of SAEs	1	4
Number of possibly related, probably related or related SAEs	0	0
Number of patients with SAE	1 (50%)	2 (67%)
Number of deaths	1 (50%)	0
Number of study discontinuation due to AEs	1 (50%)	1 (33%)
Visual disturbance	1 (50%)	0
Hepatic toxicity	1 (50%)	0

TEAE=Treatment emergent adverse event

TFF-V2-001: Mycologic assessment:

Subject	treatment	Mycologic evidence of Aspergillus infection at screening	Day 56 and Day 91 Whole blood PCR
Patient 1	oral	Positive BAL and sputum culture	Not available
Patient 2	oral	Positive BAL microscopy and whole blood PCR	negative
Patient 3	inhaled	Positive BAL culture and BAL GM= >1.0	negative
Patient 4	inhaled	Positive BAL culture	negative
Patient 5	inhaled	Positive BAL culture	negative

No Day 56 or Day 91 data from patient 201-001 due to study discontinuation due to death.

BAL=bronchoalveolar lavage; PCR=polymerase chain reaction; GM=galactomannan