LAY SUMMARY FOR TRIAL
ET-ENAC-03

FULL TITLE

A Randomised, Double-Blind, Placebo Controlled, Two-Part Study to Evaluate the Efficacy, Safety, Tolerability and Pharmacokinetics of a Repeat Dose of Inhaled ETD001 in People with Cystic Fibrosis

ABBREVIATED TITLE

A Study of ETD001 in Adults with Cystic Fibrosis

Protocol: ET-ENAC-03 Phase: 2

Compound Identifier: ETD001

Trial ID Numbers: EU CT: 2023-504092-25-00,
NCT: 06478706,
ISRCTN: 11798668

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1 WHY WAS THIS TRIAL DONE?

Cystic fibrosis (CF) is a genetic condition that causes thick, sticky mucus to build up in the lungs. This makes breathing difficult, increases infections, and leads to lung damage over time.

Treatments improved, but many people with CF still have lung problems. Many take Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) modulator medicines that help the CFTR protein move chloride and water in and out of cells to keep mucus thin. However, some people cannot take these medicines, and others may need additional treatments.

In CF, changes in the CFTR gene mean the CFTR protein may be missing, faulty, or unable to reach the cell surface. Without working CFTR mucus becomes thick and sticky, causing infections, and other complications.

ETD001 is a new inhaled medicine designed to hydrate airway mucus .

The trial was designed to find out:

- Whether ETD001 improved lung function in adults with CF
- Whether ETD001 was safe and well tolerated
- How the body absorbs and processes ETD001 after inhalation

2 HOW DOES ETD001 WORK?

People with CF often have dehydrated mucus in their airways. ETD001 is an inhaled medicine that blocks a pathway called the epithelial sodium channel (ENaC). Blocking ENaC may help keep more water in the airways, making mucus less thick and easier to remove.

Researchers believe this may help:

- Improve mucus clearance
- Reduce airway blockage
- Improve breathing
- Potentially reduce lung infections and flare-ups of CF lung disease

3 WHO TOOK PART?

71 adults with CF agreed to join the trial. They were recruited from 21 centres in France, Germany, Italy, and the UK.

Of these:

- 57 participants received trial treatment.
- 54 participants completed the trial.

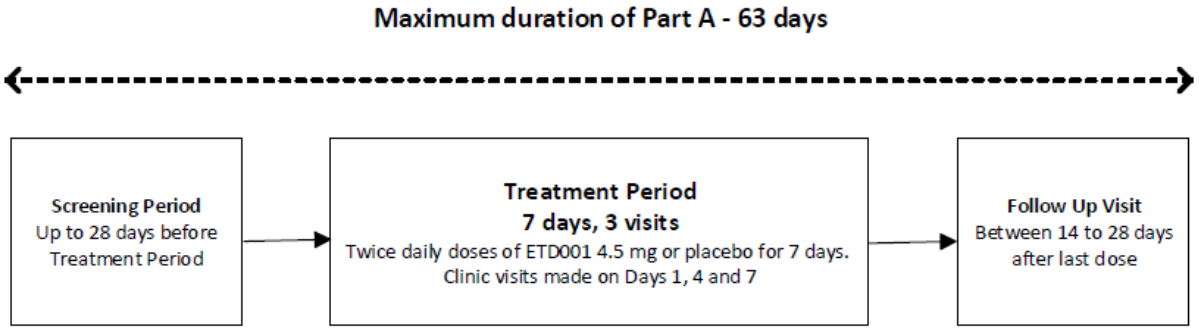
Participants were between 18 and 58 years of age and had mild to moderate lung problems caused by CF. Participants were not taking CFTR modulator therapy.

4 HOW WAS THE TRIAL CONDUCTED?

This was a Phase 2 clinical trial conducted in two parts (A and B). The trial used the following strategies to help ensure that the results were unbiased.

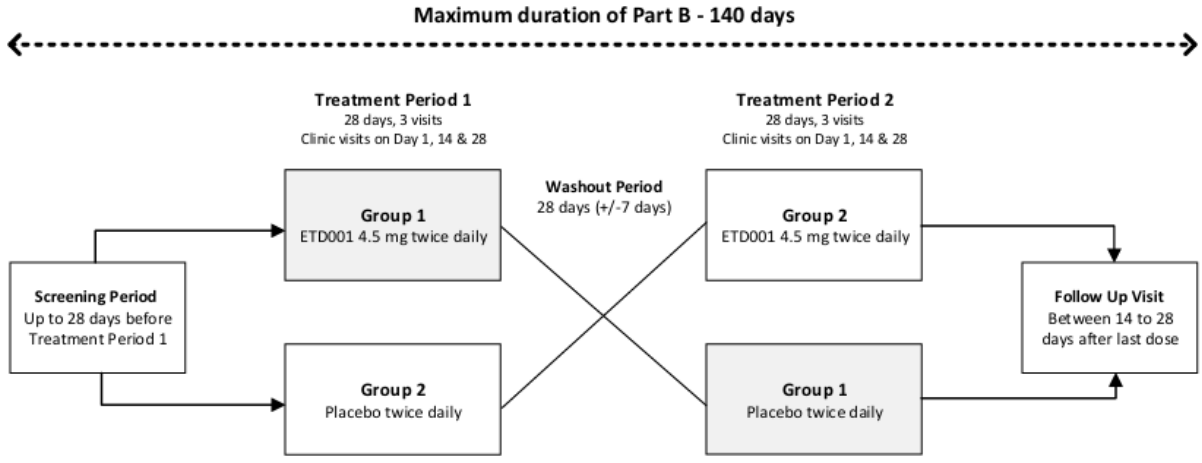
Randomisation	The choice of treatment, or the order in which treatments were received, were decided by chance.
Double-blind	Neither participants nor trial doctors knew which treatment were receiving at any point during the trial.
Placebo-controlled	A placebo looks like the trial medicine but contains no active drug.

4.1 Part A – Safety



- 10 participants received treatment, 9 participants completed all trial visits.
- Participants received either inhaled ETD001 (7 participants) or placebo (3 participants) twice daily for 6 days with 1 dose on Day 7.

4.2 Part B – Effectiveness



- 47 participants received treatment, 45 participants completed all trial visits.
- 24 participants were randomised to receive ETD001 followed by placebo; 23 participants were randomised to receive placebo followed by ETD001.
- ETD001/placebo were inhaled twice daily for 27 days with 1 dose on Day 28.

5 WHAT WAS MEASURED?

The main measurement used in the study was the predicted forced expiratory volume over 1 second (ppFEV1). The test measures how much air a person can breathe out in one second compared with expected values for healthy people of similar age, sex, and height.

An increase in ppFEV1 generally means improved lung function.

Researchers also looked at:

- Side effects
- Other lung function measurements
- Respiratory symptoms
- Clinical laboratory test results
- Vital sign monitoring results (including blood pressure, heart rate, ECG recordings)
- Drug levels in blood and urine

6 WHAT WERE THE RESULTS?

6.1 Did ETD001 Improve Lung Function?

Yes.

After 28 days of treatment, participants had better lung function when receiving ETD001 compared with placebo. The difference between ETD001 and placebo was statistically significant, meaning the result was unlikely to have occurred by chance. Researchers also considered the improvement to be clinically meaningful.

The primary analysis showed an average improvement of approximately 3.4%in ppFEV1 compared with placebo. Similar positive findings were seen in several additional analyses, giving researchers confidence in the result.

6.2 Were the Results Consistent?

Yes.

The improvement in lung function was seen across several groups of participants, including those using:

- Hypertonic saline
- Dornase alfa
- Both hypertonic saline and dornase alfa

Researchers did not find evidence that the order in which participants received ETD001 and placebo influenced the results.

6.3 What About Other Lung Function Measures?

Several additional lung function tests supported the main findings.

Researchers observed:

- Improvement in the FEV1/FVC ratio
- Positive trends in other breathing measurements

Overall, these findings supported the conclusion that ETD001 improved lung function over the 28-day treatment period.

6.4 Did Participants Report Feeling Better?

Participants completed the Cystic Fibrosis Questionnaire-Revised (CFQ-R), which measures respiratory symptoms and quality of life.

Changes in symptom scores were relatively small, but the results were generally consistent with the improvements observed in lung function tests.

7 WAS ETD001 SAFE?

Overall, ETD001 was considered safe and well tolerated.

The majority of adverse events were mild or moderate in severity. Three participants did not complete the trial. Most events were considered not related to dosing with ETD001 by the investigator.

Events that were considered possibly or probably related to dosing with ETD001 are described as adverse reactions. One participant was withdrawn because of an adverse reaction.

No participants died during the trial.

7.1 What Serious Adverse Reactions Were Seen?

Event	Related to Treatment?	Number of Events	% of Total Serious Events Reported	Withdrawn?
Shortness of breath (dyspnoea)	Probably	1	8%	Yes

7.2 What Adverse Reactions Were Seen?

Event	Number of Participants Reporting	Number of Events	% of Total Events Reported
Cough	17	228	31
Productive cough (bringing up mucus)	16	100	14
Chest tightness	6	35	5
Headache	3	13	2
Haemoptysis (coughing up bloody mucus)	3	4	0.5
Fatigue	3	3	0.4
Sore throat	2	4	0.5
Dry throat	1	56	8
Dizziness	1	8	1
Increased sputum	1	3	0.4
Dyspnoea	1	2	0.2
Bronchial obstruction	1	1	0.1
Dry mouth	1	1	0.1
Hyperkalaemia	1	1	0.1
Jaw pain	1	1	0.1
Throat pain	1	1	0.1
Upper abdominal pain	1	1	0.1

Researchers noted that increased coughing and mucus clearance may be related to the intended action of ETD001 in the lungs.

7.3 Were There Any Important Laboratory or Heart Safety Findings?

No clinically meaningful safety concerns were identified.

Researchers did not observe important changes suggesting harm to major organs, significant heart rhythm problems, or electrolyte disturbances.

8 WHAT DID RESEARCHERS LEARN ABOUT HOW THE BODY PROCESSES ETD001?

After inhalation, ETD001 could be measured in participants' blood.

The medicine:

- Reached peak blood levels between 0.5 to 2 hours after dosing
- Showed low levels of urinary excretion
- Demonstrated exposure levels consistent with previous trials in healthy volunteers

These findings suggest that ETD001 mainly acts in the lungs, as intended.

9 WHAT WERE THE LIMITATIONS OF THIS TRIAL?

The trial provides encouraging results, but some limitations should be considered:

- The number of participants was relatively small
- Treatment lasted only 28 days
- Only adults participated
- Participants were not receiving CFTR modulator therapies

Larger, longer trials will be needed to better understand:

- Long-term benefits
- Long-term safety
- Use alongside other CF therapies

10 WHAT DO THESE RESULTS MEAN?

This trial was the first clinical trial of ETD001 in people with CF (pwCF).

The results showed that:

- ETD001 improved lung function compared with placebo.
- The improvements were statistically significant and clinically meaningful.
- ETD001 was generally safe and well tolerated.

These findings provide evidence that blocking ENaC may be a promising new approach for treating CF. Further clinical trials are planned to confirm these results and determine whether ETD001 can provide long-term benefits for pwCF.