Brand Name: Symdeko®

Generic Name: Tezacaftor-Ivacaftor

Manufacturer: Vertex Pharmaceuticals Inc. (1)

Drug Class: Cystic fibrosis transmembrane conductance regulator (CFTR) gene modulator (1-4).

Uses:

Labeled: Cystic fibrosis; F508del mutation or with another responsive gene mutation (1-4).

Unlabeled: N/A

Mechanism of action: Symdeko is a combination of tezacaftor and ivacaftor. Tezacaftor works by increasing the cell's ability to produce normal CTFR protein, along with select types of other CDFR mutations. Ivacaftor operates by increasing the opening of CTFR channels. This results in an overall increase of chloride transport (1-4).

Pharmacokinetics:

Absorption:

Tezacaftor – Absorption does not vary when consumed with fatty foods, or during fasting (1-4).

Ivacaftor – Absorption increases 3-fold with fat containing foods (1-4).

Category	Tezacaftor	Ivacaftor
Tmax	4 hours	6 hours
Volume of dist.	271 L	206 L
Half life	15 hours	13.7 hours
Clearance	1.31 L per hour	15.7 L per hours
Protein binding	99% bound to albumin	99% bound to alpha 1-acid glycoprotein and albumin
Bioavailability	84.5%	11.3%

Metabolism

Tezacaftor – majority of metabolism occurs hepatically by CYP enzymes 3A4 and 3A5. This process produces metabolites M1, M2, and M5. Metabolite M1 has been found to be as active as the parent drug, M2 is considered to be weakly active, and M5 is inactive (1-4).

Ivacaftor – metabolism of ivacaftor occurs in the liver by CYP enzymes 3A4 and 3A5, creating metabolites M1 and M6. M1 is thought to be much less active than the parent drug and M6 an inactive metabolite (1-4).

Elimination

Tezacaftor – The majority of elimination occurs through the fecal route (72%) with 14% being eliminated through the kidney (< 1% excreted as unchanged) (1-4).

Ivacaftor –The majority of elimination occurs through the fecal route (87.8%), with 6.6% eliminated through the kidney (1-4).

Efficacy and Safety Studies

Rowe S.M., *et al.* Tezacaftor–Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis**.** N Engl J Med. 2017 377:2024-2035

Study design

Randomized, double blind, placebo controlled, phase 3, crossover trial.

Description of study

Methods: Patients with Cystic Fibrosis who are heterozygous for Phe508del CFTE mutation and a second allele with residual function were included in this study. The study included 3 possible treatment arms: tezacaftor 100mg-ivacaftor 150mg and ivacaftor 150mg 12 hours later, ivacaftor 150mg monotherapy, or placebo. Participants were randomly selected to receive 2 of the 3 treatments, each treatment period lasted eight-weeks and was then separated by an eight-week washout period. The primary end point was the absolute change in FEV1 percentage from baseline to the mean FEV1 of weeks 4 and 8. Secondary end points included change in cystic fibrosis questionnaire-revised, change in sweat chloride concentration, and safety. *Results:* 246 patients underwent randomization. The primary outcome showed an increase in FEV1 by 6.8% (95%[CI] 5.7-7.8) in the tezacaftor-ivacaftor group, where as the ivacaftor-only group reported an increase in 4.7% (95%[CI] 3.7-5.8)(p = <0.001) compared to placebo. Differences between tezacaftor-ivacaftor and ivacaftor-monotherapy were not statistically significant. Change in

CFG-R respiratory domain score in the tezacaftor-ivacaftor group and the ivacaftor-monotherapy groups showed statistical and clinical significant benefits over placebo, but not between the two treatment groups. Absolute changes in sweat chloride concentration when compared to placebo were -9.5 mmol/L (-11.7 to -7.3) for tezacaftor-ivacaftor, -4.5 mmol/L (-6.7 to -2.3) for ivacaftor-monotherapy, and the difference between the two treatment groups were trendingtowards improved sweat chloride improvement for the tezacaftor-ivacaftor group over the ivacaftor-monotherapy group but no statistical significance was calculated. No deaths occurred during the study, and 3 patients dropped out (2 in the ivacaftor-monotherapy group and 1 in the placebo group). Adverse events that that occurred more commonly in the tezacaftor-ivacaftor group over placebo were diarrhea, headache, increased sputum production, and nasopharyngitis.

Limitations

Demographic information was provided for the first period, however, the authors omitted information for the second period leaving the reader to assume that there was no difference.

Neither compliance nor unblinding was discussed in the study.

Available literature states that fatty foods increase ivacaftor absorption by 3 fold. The authors did not mention restrictions on diet or use of any food diaries. This could have greatly impacted the efficacy of both treatment groups.

While the use of a crossover design is adequate, it is not the preferred method. The best study design would have been for the authors to have individual groups of tezacaftor-ivacaftor, ivacaftor monotherapy, and placebo. Coupled with an appropriate sample size, this would have been the preferred way of designing the study.

Funding for this study came from Vertex, who is the manufacturer of tezacaftor-ivacaftor. This increases the risk of bias as the authors may want to present the results in a way to enhance the results of tezacaftor-ivacaftor.

Conclusion

The results of this study indicate that tezacaftor-ivacaftor is significantly more effective than placebo and ivacaftor-monotherapy in raising FEV1 in patients that are heterozygous for Phe508del mutations and an additional residually functioning gene. Tezacaftor-ivacaftor is also trending towards a improved quality of life and a greater reduction in sweat chloride concentrations over ivacaftor-monotherapy. No major adverse effects were associated with tezacaftor-ivacaftor outside of what would be normal for patients with cystic fibrosis (i.e. infective pulmonary exacerbation, increased sputum, and cough).

Donaldson S.H., *et al.* Tezacaftor/Ivacaftor in Subjects with Cystic Fibrosis and *F508del*/*F508del-CFTR* or *F508del*/*G551D-CFTR*. Am J Respir Crit Care Med. 2018. 197(2): 214–224

Study design

Randomized, placebo-controlled, double blind, multicenter phase 2 proof-of-concept study.

Description of study

This study enrolled 131 participants who have a diagnosis of Cystic Fibrosis. The study design consisted of 14 treatment arms aimed at determining the most effective regimen with the least amount of adverse effects. The first group set out to determine the most effective strength. This included the following dose regimens: placebo, tezacaftor 10mg qd, tezacaftor 30mg qd, tezacaftor 100mg qd, tezacaftor 150mg qd, tezacaftor 10mg qd with ivacaftor 150mg q12h, tezacaftor 30mg qd with ivacaftor 150mg q12h, tezacaftor 100mg qd with ivacaftor 150mg q12h, and tezacaftor 10mg qd with ivacaftor 150mg q12h. The next group was designed to find the best dose regimen. The following regimens were included: tezacaftor 100mg qd with ivacaftor 150mg q12h, tezacaftor 100mg qd with ivacaftor 50mg q12h, tezacaftor 50mg qd with ivacaftor 150mg q12h, and placebo. Finally, the authors wanted to test for efficacy against the f508del/G551D mutation, for which they used tezacaftor 100mg qd with ivacaftor 150mg q12h against an active control (ivacaftor 150mg q12h). Study participants (n=131) were randomized at a 4:1 ratio and received their medication/placebo for the following 28-day period. During which time the authors analyzed changes in FEV1 and sweat chloride concentrations, from baseline. *Results:* When comparing the effects of different doses of tezacaftor the authors found that tezacaftor 100mg-ivacaftor 150 mg q12h was the most effective at increasing FEV1 and decreasing sweat chloride ($p = < 0.05$). After administering the last dose, participants entered a 28-day monitoring period without treatment. Participants were then evaluated for the last time and found that FEV1 and sweat chloride returned to baseline levels. Meaning that any benefit recorded during the trial was due to the treatment. Safety outcomes determined that the majority of the events were disease related. The authors did note that those taking tezacaftor experienced cough, nausea, fatigue, and increased sputum more commonly than the placebo group.

Limitations

Do to the number of treatment arms used in the study; each group included a small number of participants. Therefore while the objectives and methods for the study were appropriate, the study itself was significantly underpowered.

Participants in the study were also started on ivacaftor 28 days prior to the start of the study, and continued taking it throughout the study

duration. It was unclear exactly how this factored into the results of the study and requires more information from the authors.
Funding was provided by the manufacturer of tezacaftor-ivacaftor, which increases the chance of bias in the study.

Conclusion:

Despite the small sample size, the authors were able to conclude that the use of tezacaftor 100mg-Ivacaftor 150mg once daily followed by ivacaftor 150mg 12 hours later is the optimal dose for patients to use when treating cystic fibrosis F508del and G551D mutations.

Taylor-Cousar J.L., *et al* Texacaftor-Ivacaftor in patients with Cystic Fibrosis Homozygous for Phe508del. N Eng. J Med. 337;21: 2013-23

Study design

A phase 3 randomized, double blind, multicenter, placebo-controlled, parallel-group trial.

Description of study

Methods: 509 participants (251 study group and 258 placebo) receiving either tezacaftor 100mg-ivacaftor 150mg daily and a second dose of ivacaftor 150mg 12 hours later, or a matched placebo. The primary outcome of the study was the change in absolute percentage in FEV1 from baseline through week 24. Secondary endpoints were changes in BMI, number of pulmonary exacerbations, changes in the domain score of the cystic fibrosis questionnaire-revised, and safety. *Results:* The study showed that the use of tezacaftor-ivacaftor significantly improved the percentage points of absolute FEV1 over a 24-week period compared to placebo (4.0 percentage points; 95% CI, 3.1 to 4.8; P = <0.001). The number of pulmonary exacerbations that led to treatment with antibiotics was significantly lower in the tezacaftor-ivacaftor group than the placebo (Hazard ratio 0.64; 95% CI, 0.46 to 0.88). There were no clinical or statistical significant differences in BMI. Changes in CFQ-R domain score were 5.1 (95% CI, 3.2 to 7.0) in favor of tezacaftor-ivacaftor. Of the adverse events reported, the following occurred more commonly in the tezacaftor-ivacaftor group; headache, nausea, and nasopharyngitis.

Limitations:

There was also no mention of compliance or the steps taken by the authors to ensure that the volunteers were taking the medication. The literature mentions that fatty foods can increase the absorption of ivacaftor. Thus, it would make sense for the authors to either standardize the participant's diet, or have them keep a food diary throughout their study.

Funding for this study was provided by Vertex, who is the manufacturer of tezacaftor-ivacaftor. This increases the chance of misleading results as the authors may initiate steps in order to ensure that the tezacaftor-ivacaftor group shows significant benefit.

Conclusion

The results of this study indicate that the use of tezacaftor 100mg/ivacaftor150mg once daily followed by ivacaftor 150mg 12 hours later is superior to the matched placebo utilized in the study. The improved FEV1 by 4% is clinically significant given that the average cystic fibrosis patient loses 3% of their lung function each year. Tezacaftor-ivacaftor shows promise that it can provide benefit to those who take it, and warrants further studies to confirm these findings.

Contraindications:

- Not reported

Precautions:

- Use with strong CYP3A inducers are not recommended. As this can result in sub-therapeutic concentrations of Symdeko® (1-4).
- Liver enzymes (ALT and AST) should be checked every three months during the first year of treatment, then yearly thereafter. Patients found to have liver enzymes greater than five times the normal limit, or three times the limit with bilirubin levels 2 times the normal limit should consider discontinuing Symdeko® (1-4).
- Cataracts have been reported in pediatric patients started on Symdeko®. It is recommended to schedule eye exams for pediatric patients starting Symdeko® (1-4).

Adverse Effects:

≥ 1% incidence

- Nausea, dizziness, headache, and congestion of nasal sinuses (1-4).

Serious adverse events (<1% incidence)

- Distal intestinal obstruction syndrome (0.6% incidence) (1-4).
- Increased liver enzymes
- Cataracts

Drug Interactions:

- **Moderate CYP3A enzymes inhibitors** (i.e. erythromycin, verapamil, diltiazem, cyclosporine, ciprofloxacin, fluvoxamine, fluconazole, aprepitant, imatinib, Nilotinib, dronedarone, crizotinib, and atazanavir)

may impair metabolism of tezacaftor and ivacaftor resulting in a higher concentration.

- Conivaptan is a strong CYP3A inhibitor and may increase ivacaftor concentrations.

- Strong CYP3A inducers (i.e. phenytoin, carbamazepine, rifampin, mitotane, fosphenytoin, St. John's wort, and enzalutamide) may increase the metabolism of tezacaftor and ivacaftor resulting in a sub-therapeutic levels.

Dosing/Administration: (1-4)

Usual – Take one tezacaftor 100 mg-ivacaftor 150 mg tablet each morning, then take one ivacaftor 150mg tablet by mouth in the evening. Both medications should be taken with fat containing foods.

Geriatric – There is no data available to assess proper dosing of Symdeko® in patients ≥ 65 years of age.

Pediatric – take one tablet of tezacaftor 100mg-ivacaftor 150mg by mouth each morning, then take ivacaftor 150mg in the evening. Both medications should be taken with fat containing foods.

Renal impairment – no change is necessary

Hepatic impairment – (based on the Child-Pugh score)
- Class A (mild) = no change necessary
- Class B (moderate) = take tezacaftor 100mg/ivacaftor 150mg each morning
- Class C (severe) = tezacaftor 100mg/ivacaftor 150 mg each morning or less depending on physician orders

Use in Special circumstances:

Pregnancy and lactation: Pregnancy and lactation data for Symdeko® is lacking. (2-4). Current data is based on animal studies (rats and rabbits) and has shown no significant teratogenic or adverse effects in offspring (1).

Conclusion:

Based on available information, the use of Symdeko® for the treatment of cystic fibrosis should be considered as safe and effective. Symdeko® has demonstrated superiority over ivacaftor monotherapy and placebo by

increasing FEV1, quality of life, and decreasing chloride concentration in sweat. Tezacafot-ivacaftor is not the first of its class, and comparative studies between Symdeko® and lumacaftor-ivacaftor must be done in order to determine superiority or non-inferiority. Cost-effectiveness studies are also necessary as Cystic Fibrosis medications are associated with a high cost burden.

Recommended references:

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4. Tezacaftor-Ivacaftor. Clinical Pharmacology [Internet database]. Gold Standard, Inc., 2007. Available at: http://www.clinicalpharmacology.com. Accessed: August 15, 2018
5. Rowe S.M., *et al.* Tezacaftor–Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis. N Engl J Med. 2017 377:2024-2035
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7. Taylor-Cousar J.L., *et al* Texacaftor-Ivacaftor in patients with Cystic Fibrosis Homozygous for Phe508del. N Eng. J Med. 337;21: 2013-23

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