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Aclidinium: A New Long-acting Anti-cholinergic Inhaler for COPD

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Chronic Obstructive Pulmonary Disease (COPD) affects an estimated 6.3% of the adult population of the United States.[1] That equates to about 15 million adults diagnosed with COPD and millions more that may not be aware of their condition. Chronic lower respiratory disease, including COPD, remains the third leading cause of death in the United States in 2010.[2] Smoking tobacco has been associated with 85% of diagnoses and is the number one avoidable risk factor for developing COPD.[3,4] Therefore, cessation of smoking is pivotal to the prevention and treatment of the disease.[3] The cost of COPD in the United States in 2010 is estimated to be 50 billion dollars in combined direct and indirect medical expenses.[5]

COPD is a disease that has historically been divided into two categories, chronic bronchitis or chronic emphysema. Chronic emphysema is characterized by destruction of alveoli and alveolar attachments, which leads to decreased elastic recoil of the lungs and impaired gas exchange.[6] Chronic bronchitis is characterized by excessive cough and sputum production for at least 3 months in each of 2 consecutive years.[6] Most patients with COPD will present with a mixture of each category.[6] Classic symptoms of COPD include chronic cough, shortness of breath, and excessive sputum production.[4] Spirometric diagnosis is done using the forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ratio. A post-bronchodilator FEV_1/FVC ratio less than 0.70 is indicative of airflow obstruction and is diagnostic of COPD.[6]

One main class of drugs used to treat COPD is the inhaled anti-cholinergics. The primary muscarinic receptors involved in bronchial constriction are M_1, M_2, and M_3 type receptors.[7] Studies have shown that M_3 type receptors play the largest role in tracheal and bronchial constriction.[8] Agonism of M_1 and M_3 receptors cause bronchoconstriction, while agonism of presynaptic M_2 receptors causes inhibition of acetylcholine release.[4] The M_2 receptors act as auto-receptors and serve to limit acetylcholine induced bronchoconstriction.[9] However, the clinical importance of the M_2 receptor subtype in COPD has not been adequately established.[7]

Beta-2 adrenergic agonists also play a large role in treating COPD. Beta-2 agonists cause bronchodilation by increasing the production of cyclic AMP in bronchial smooth muscle, causing relaxation and subsequent dilation of airways.[6] Short-acting beta-2 agonists are used as a rescue medication, while long-acting beta-2 agonists are used as a maintenance therapy.

Forest Pharmaceuticals, Inc. obtained FDA approval of Tudorza Pressair® (aclidinium bromide inhalation powder) in July 2012. It is an inhaled anticholinergic medication approved for long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease.[10] It is not intended for use as a rescue inhaler for acute symptoms. This article will outline the pharmacology, pharmacokinetics, clinical trials, adverse effects, dosing, and cost of aclidinium.

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Aclidinium acts as an antagonist at M_1 through M_5 receptors with similar potency across receptor types. Antagonism of primarily M_3 muscarinic receptors leads to bronchodilation.[4] Aclidinium shows similar binding affinities compared to tiotropium and increased potency compared to ipratropium (**Table 1**).[11] Aclidinium has a slow dissociation from the M_3 receptor, which is reflected in its long residence half-life (**Table 2**).[11] This pharmacokinetic parameter allows aclidinium to be a long acting, maintenance bronchodilator for COPD.

The bioavailability of aclidinium is 6% after inhalation.[10] Metabolism of aclidinium is mainly through enzymatic and chemical hydrolysis in plasma, which occurs very rapidly.[10] Neither of the metabolites' display any pharmacologic activity.[10] The rapid rate of metabolism of aclidinium could provide benefit in limiting systemic anticholinergic side effects such as constipation or urinary retention. *In vitro* studies show that neither aclidinium nor its metabolites show any inhibition of CYP450 enzymes at concentrations 1,000 fold higher than the expected plasma concentrations.[10] However, no formal drug interaction studies have been performed.[10]

Table 1: Binding affinity of aclidinium, ipratropium, and tiotropium for human M_1, M_2, M_3, M_4, and M_5 receptors[11]

	Muscarinic Receptor Subtype Binding Affinity (K_i)				
Compound	M_1	M_2	M_3	M_4	M_5
		nM			
Aclidinium	0.10 ± 0.00	0.14 ± 0.04	0.14 ± 0.02	0.21 ± 0.04	0.16 ± 0.01
Ipratropium	1.31 ± 0.15	1.12 ± 0.13	1.24 ± 0.08	1.92 ± 0.18	3.22 ± 0.15
Tiotropium	0.13 ± 0.00	0.13 ± 0.04	0.19 ± 0.04	0.30 ± 0.09	0.18 ± 0.06

M_1= muscarinic acetylcholine receptor subtype 1, *nM*= nanomolar
*Lower K_i indicates increased binding affinity

Clinical Trials

The safety and efficacy of aclidinium was assessed in one phase II trial and three phase III trials (**Table 3)**. Optimal dosing was established during the phase II trial,[12,13] while efficacy was established in the 3 phase III trials.[13-15] The inclusion and exclusion for these trials were almost completely identical. These trials enrolled males and females who were at least 40 years of age, had a clinical diagnosis of moderate to severe COPD, had a 10-pack year history of smoking or was an active smoker at enrollment, had a post-albuterol FEV_1/FVC ratio of less than 70%, and had a 10-15 minute post-albuterol inhalation FEV_1 value between 30-80% of predicted FEV_1 value.[12-15] These trials excluded patients with a history or current diagnosis of asthma, other significant respiratory illness at time of enrollment, hospitalization in past 3 months due to COPD, signs of COPD exacerbation or respiratory infection within 6 weeks prior to enrollment, significant cardiovascular conditions, presence of symptomatic benign prostatic hyperplasia (BPH) or narrow-angle glaucoma, and QTc interval of greater than 470 milliseconds at time of screening visit.[12-15]

The phase II dose ranging trial (LAS29)[12,13] was a randomized, double-blind, placebo-controlled, active-controlled, cross-over trial. It was conducted at 10 different sites in Germany and 1 in Belgium and it enrolled a total of 79 patients. The treatment groups consisted of aclidinium 100mcg twice daily, 200mcg twice daily, 400mcg twice daily, formoterol 12mcg twice daily as an active control, and a placebo controlled group. Each treatment period was 7 days in length, followed by a 5-7 day wash out period before starting the next treatment. Each study subject cycled through each of the different treatment arms. The primary outcome was the change in baseline FEV_1 at 0-12 hours on day 7 of each treatment period. Secondary outcomes included change from baseline FEV_1 values at 12-24 hours on day 7 of treatment, change in base-

Table 2: Association rate and dissociation kinetic parameters of [^{3}H]aclidinium, [^{3}H]ipratropium, and [^{3}H]tiotropium to human M_3 receptors[11]

	M_3 Receptor		
Compound	***K* on (M^{-1} x min^{-1})**	***K* off (min^{-1})**	***t* 1/2 (*h*)**
Aclidinium	$1.4 \times 10^8 \pm 5.8 \times 10^6$	0.02 ± 0.00	29.24 ± 0.61
Ipratropium	$1.1 \times 10^8 \pm 9.1 \times 10^6$	1.49 ± 0.06	0.47 ± 0.02
Tiotropium	$5.5 \times 10^7 \pm 4.8 \times 10^6$	0.011 ± 0.00	62.19 ± 2.96

h = hours, *M* = molar concentration, M_3 = muscarinic acetylcholine receptor subtype 3, *min* = minutes
*For K_{on}, larger number means slower onset of action
*For K_{off}, smaller number means longer duration of action
*$T_{1/2}$ reflects residence half-life at receptor

Table 3: Summary of Phase III Clinical Trials for Aclidinium

Study	Intervention	Primary Outcome			
		Change from baseline trough FEV_1 at week 12 (mL)	Treatment difference from placebo (mL)	Change from baseline trough FEV_1 at week 24 (mL)	Treatment difference from placebo (mL)
ACCORD COPD I, Kerwin (2012)[14]	Acl 200mcg BID (N=184) Acl 400mcg BID(N=190) Pcb (N=186)	61 99 -25	86 (p<0.001) 124 (p<0.001)	N/A	N/A
ACCORD COPD II[13, ¥]	Acl 200mcg BID (N=185) Acl 400mcg BID (N=177) Pcb (N=182)	43 64 -8	51 (p=0.019) 72 (p=0.001)	N/A	N/A
ATTAIN, Jones (2012)[15]	Acl 200mcg BID (N=277) Acl 400mcg BID (N=269) Pcb (N=273)	30 58 -47	77 (p<0.001) 105 (p<0.001)	26 66 -73	99 (p<0.0001) 128 (p<0.0001)

Acl = aclidinium, BID = twice daily dosing, FEV_1 = Forced expiratory volume in 1 second, mL = milliliters, Pcb = Placebo
¥, Trial not formally published. Results from FDA medical review.

line FEV_1 at 0-24 hours on day 7 of treatment, and change from baseline in morning pre-dose FEV_1 on day 7 of treatment.

The difference in FEV_1 relative to placebo on day 7 at 0-12 hours for aclidinium 100mcg twice daily, 200mcg twice daily, 400mcg twice daily, and formoterol 12mcg twice daily were 154 mL, 176 mL, 208 mL, and 210 mL, respectively.[13] Each of these treatment arms were statistically significant compared to placebo (p<0.0001).[13] Statistical tests comparing active drug treatment arms were not reported. This trial established 400mcg of aclidinium twice daily as an effective dose and supported its evaluation in phase III clinical trials.

The ACCORD COPD I[14] trial was a 12 week, phase III trial that assessed the efficacy and safety of aclidinium versus placebo. It was conducted at 106 different sites in the United States and Canada. The trial evaluated aclidinium 200mcg twice daily (N=184), aclidinium 400mcg twice daily (N=190), and placebo (N=186). The primary endpoint was change from baseline in pre-dose FEV_1.

At week 12, both the 200mcg and 400mcg twice daily dose of aclidinium bromide showed statistically significant improvement in the primary outcome relative to placebo.[14] The 200mcg dose of aclidinium improved trough FEV_1 relative to placebo by 86 mL (p<0.001) and the 400mcg dose improved trough FEV_1 by 124 mL (p<0.001). Patient quality of life (QOL) was also assessed using the St. George's Respiratory Questionnaire (SGRQ).[16] The SGRQ is a 50 question assessment used by clinicians to gauge the impact of asthma or COPD on a patient's quality of life. The higher the score, the more impact the disease has on the patient's life. Reduction of SGRQ score implies improvement in a patient's quality of life. At the end of the 12 weeks, both doses of aclidinium reduced SGRQ score by about 4.5 points compared to baseline (p<0.05).[14] However, compared to placebo, the two treatment groups didn't reach the minimum clinically important difference (MCID) of ≥4 as suggested by the SGRQ. Aclidinium 200mcg and 400mcg reduced the use of a rescue inhaler versus placebo by 0.7 puffs/day (p=0.001) and 0.9 puffs/day (p<0.0001), respectively.

Changes in FEV_1 occurred rapidly following the first dose of aclidinium 200mcg and 400mcg and was maintained throughout the 12 week trial. On day one thirty minutes after the first dose, aclidinium 200mcg and 400mcg had increased peak FEV_1 relative to placebo by 89mL and 125mL, respectively (p<0.0001 for both).[14] At week 12 aclidinium 200mcg and 400mcg improved peak FEV_1 relative to placebo by 146mL and 192mL, respectively (p<0.0001 for both). Aclidinium appears to reach its maximum effect after the first dose, which could increase patient compliance as they would experience the benefits at the beginning of treatment. Clinicians could also assess whether or not the patient will respond to aclidinium by administering a test dose in clinic and measuring pulmonary response. Potential limitations of ACCORD COPD I[14] include relatively short duration of the trial (12 weeks) and the primarily Caucasian patient population (93.8%).

The ACCORD COPD II[13] trial was a 12 week, phase III trial that evaluated safety and efficacy of aclidinium versus placebo. This trial was almost identical to the study design of ACCORD COPD I. It was conducted at 112 different sites across the United States and Canada. It evaluated the effectiveness of aclidinium 200mcg twice daily (N=185), aclidinium 400mcg twice daily (N=177), and placebo (N=182). The primary endpoint was change from baseline in

pre-dose FEV_1 at week 12.

At week 12, aclidinium 400mcg twice daily significantly improved baseline pre-dose FEV_1 versus placebo by 72 mL (p=0.001) and aclidinium 200mcg twice daily significantly improved baseline pre-dose FEV_1 versus placebo by 51mL (p=0.019).[13] The effect of aclidinium 400mcg twice daily compared to placebo on baseline FEV_1 at 12 weeks was smaller in this trial than what was observed in ACCORD COPD I[14] (72 mL vs. 124 mL). The authors attributed this smaller effect size due to the difference in severity of COPD patients in baseline between the two trials.[13] In ACCORD COPD II[13], 54.2% of patients in the aclidinium 400mcg twice daily arm were classified at stage III COPD (severe), while 36.8% in the placebo arm were classified at stage III.[18] In ACCORD COPD I[14], 38.9% in the placebo arm were stage III, while 35.8% in the aclidinium 400mcg twice daily were stage III.[13] The rest of these patients were classified at stage II COPD (moderate). Therefore, there were a higher percentage of sicker patients in ACCORD COPD II[13] in the aclidinium arm versus the placebo arm. Limitations of this trial include the relatively short duration (12 weeks), primarily Caucasian population (93%), and the difference in baseline COPD severity as noted previously.

The ATTAIN[15] trial was the largest and longest trial in this series. It was a 24 week, phase III trial that assessed the safety and efficacy of aclidinium 200mcg twice daily (N=277), aclidinium 400mcg twice daily (N=269), and placebo (N=273). This study was conducted at 103 different sites in 11 different countries. The primary outcome of this study was the change from baseline in pre-dose FEV_1 at 24 weeks.

At 24 weeks, change from baseline pre-dose FEV_1 for aclidinium 200mcg and 400mcg relative to placebo were 99mL (p<0.0001) and 128mL (p<0.0001) , respectively.[15] As seen in ACCORD COPD I[14], this trial also demonstrated a maximum effect of aclidinium reflected in peak FEV_1 after the first dose. Aclidinium 400mcg increased peak FEV_1 compared to placebo after the first dose by 187mL (p<0.0001) and this benefit was maintained until the end of the 24 weeks as reflected in the peak FEV_1 increase of 209mL (p<0.0001). There was a statistically significant decreased use of albuterol rescue inhaler in the aclidinium group at 24 weeks. Aclidinium 400mcg twice daily decreased the use of albuterol use by 34% (p<0.0045) from 3.5 puffs/day at the beginning of the study to 2.3 puffs/day at 24 weeks. Placebo reduced albuterol use by 7% from 3.8 puffs/day at baseline to 3.55 puffs/day at 24 weeks. Patient QOL was also assessed using the SGRQ. At week 24, the improvement over placebo in SGRQ score was -3.8 for aclidinium 200mcg (p<0.001) and -4.6 for aclidinium 400mcg (p<0.0001).[15] The 400mcg dose of aclidinium showed a MCID of ≥4, which represents a clinically relevant difference versus placebo. A limitation of this study is the primarily Caucasian population (95.2%) similar to the other aclidinium trials.

Adverse Events and Safety

The adverse events reported in ACCORD COPD I[14], ACCORD COPD II[13], and ATTAIN[15] trials that occurred in a frequency greater than 1% or greater versus placebo were headache, nasopharyngitis, cough, diarrhea, sinusitis, rhinitis, toothache, experiencing a fall, and vomiting (**Table 4**).[10] Three trials assessed long-term safety of aclidinium 400mcg twice daily. Two of these trials were extensions of the 3 month efficacy trials and the other was a trial dedicated to long-term safety surveillance. A total of 891 patients were followed from 40 to 52 weeks.[10] Adverse effects reported in these trials were similar to those found in the original clinical trials.[10] Withdrawal rates due to adverse effects were similar across treatment and placebo groups. Systemic anticholinergic side effects were not observed in clinical trials, possibly due to rapid metabolism of aclidinium when it enters the systemic circulation.

Dosing & Administration

Aclidinium is available as preloaded inhaler with a numerical dose indicator. It does not require placing capsules into the inhaler for each dose, as it is self-contained and ready to use right out of the packaging. Patients will also hear a "click" sound, which lets them know they are using the inhaler correctly.[10] The only FDA approved dose of aclidinium is 400mcg inhaled twice daily. Each actuation delivers 375mcg of aclidinium bromide powder to the patient.[10] There are

Table 4: Adverse Reactions From 3 Phase III Clinical Trials[10]

Adverse Reaction	Aclidinium 400mcg BID (N=636)	Placebo (N=640)
Headache	42(6.6%)	32(5.0%)
Nasopharyngitis	35(5.5%)	25(2.9%)
Cough	19(3.0%)	14(2.2%)
Diarrhea	17(2.7%)	9(1.4%)
Sinusitis	11(1.7%)	5(0.8%)
Rhinitis	10(1.6%)	8(1.2%)
Toothache	7(1.1%)	5(0.8%)
Fall	7(1.1%)	3(0.5%)
Vomiting	7(1.1%)	3(0.5%)

no dose adjustments necessary in elderly or patients with renal impairment.[10] It has not been studied in patients with hepatic impairment, nor has the safety and efficacy been studied in children or adolescents.[10] Therefore, use in these populations is not recommended at this time.

Cost

The current average cost of Tudorza Pressair® is 262.64$ ($246.88-$273.69) for a 30 day supply containing 60 actuations. This average was collected from 4 different community pharmacies. With the Tudorza Pressair® instant savings program, patients can save up to 75$ off of their copay. The program cannot be used by anyone with government sponsored insurance (i.e. Medicare, Medicaid).

Summary

Aclidinium bromide is a new anti-cholinergic inhaler used for long-term maintenance of COPD symptoms. It provides prescribers with a second long-acting anticholinergic option to manage patients' COPD. The ACCORD COPD I[14], ACCORD COPD II[13], and ATTAIN[15] trials established safety and efficacy of aclidinium in 1,933 patients with COPD. All 3 trials showed significant improvements relative to placebo in pre-dose trough FEV_1 at the end of each respective study. Adverse effects were fairly mild and discontinuation of treatment was similar between aclidinium and control.[11-13] Systemic anti-cholinergic side effects were not observed in clinical trials, most likely due to the very short plasma half-life of aclidinium and inactivity of its metabolites. Aclidinium does not require placing a capsule into the actuator for each dose, which could provide some benefit in the elderly population that has limited dexterity.

References

1. Centers for Disease Control and Prevention. Chronic Obstructive Pulmonary Disease (COPD). http://www.cdc.gov/Features/COPDAdults/ (accessed 2013 Mar 26)
2. Centers for Disease Control and Prevention. Chronic Obstructive Pulmonary Disease (COPD). http://www.cdc.gov/injury/wisqars/pdf/10LCID_All_Deaths_By_Age_Group_2010-a.pdf (accessed 2013 Mar 26)
3. American Lung Association. Chronic Obstructive Pulmonary Disease (COPD) Fact Sheet. http://www.lung.org/lung-disease/copd/resources/facts-figures/COPD-Fact-Sheet.html
4. Williams DM, Bourdet SV. Chapter 34. Chronic Obstructive Pulmonary Disease. In: Talbert RL, DiPiro JT, Matzke GR, Posey LM, Wells BG, Yee GC, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 8th ed. New York: McGraw-Hill; 2011. http://www.accesspharmacy.com/content.aspx?aID=7975888. Accessed March 28, 2013..
5. American Lung Association. Trends in COPD (Chronic Bronchitis and Emphysema): Morbidity and Mortality. http://www.lung.org/finding-cures/our-research/trend-reports/copd-trend-report.pdf
6. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. NHLBI/WHO workshop report. Bethesda, MD: National Heart, Lung, and Blood Institute; April 2001. Updated November 2009, *http://www.goldcopd.com/*
7. Gosens R, Zaagsma J, Meurs H, Halayko AJ. Muscarinic receptor signaling in the pathophysiology of asthma and COPD. Respiratory Research 2006;7:73
8. Brown JH, Laiken N. Chapter 9. Muscarinic Receptor Agonists and Antagonists. In: Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12nd ed. New York: McGraw-Hill; 2011. http://www.accesspharmacy.com/content.aspx?aID=16660596. Accessed April 2, 2013.
9. Costello RW, Jacoby DB, Fryer AD. Pulmonary neuronal M2 muscarinic receptor function in asthma and animal models of hyperreactivity. Thorax 1998;53:613-6.
10. Product information. Tudorza Pressair® (aclidinium bromide inhalation powder). St. Louis, MO: Forest Pharmaceuticals, Inc. July 2012
11. Gavalda A, Miralpeix M, Ramos I, et al. Characterization of aclidinium bromide, a novel inhaled muscarinic antagonist, with long duration of action and a favorable pharmacological profile. J Pharmacol Exp Ther 2009;331:740–751.
12. Forest Pharmaceuticals Inc.; Efficacy and Safety of Three Doses of Aclidinium Bromide Compared to Placebo and to an Active Comparator in Chronic Obstructive Pulmonary Disease (COPD) Patients. http://clinicaltrials.gov/ct2/show/record/NCT01120093?term=aclidinium&rank=11
13. Food and Drug Administration. Medical Review. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202450Orig1s000MedR.pdf (accessed 2013 Apr 8)
14. Kerwin EM, D'Urzo AD, Gelb AF, Lakkis H, Garcia Gil E, Caracta CF; ACCORD I study investigators. Efficacy and safety of a 12-week treatment with twice-daily aclidinium bromide in COPD patients

(ACCORD COPD I). COPD 2012;9:90-101.
15. Jones PW, Singh D, Bateman ED, et al. Efficacy and safety of twice-daily aclidinium bromide in COPD patients: the ATTAIN study. Eur Respir J 2012;40:830-6.
16. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure for chronic airflow limitation - the St George's Respiratory Questionnaire. Am Rev Respir Dis 1992;145:1321-1327.

Canagliflozin: A New Type 2 Diabetes Drug with a Novel Mechanism of Action

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As of 2010, the Center for Disease Control and Prevention (CDC) estimates that diabetes affects approximately 8.3% of the United States population.[1] From 1995 to 2010 the prevalence of diagnosed diabetes in adults has risen 82% in the United States overall, with an increase of at least 100% in 18 states. Furthermore, this startling trend is present in all age groups, races, and geographic areas.[2]

Of the 25.8 million adults diagnosed with diabetes, 90 to 95% are type 2 diabetics.[1] This disease is often attributed to over-nutrition and genetic factors, ultimately leading to insulin resistance and eventually insulin deficiency. The loss of metabolic homeostasis results in high serum glucose levels.[3] Chronic increase in circulating glucose can increase the risk for long-term microvascular complications (neuropathy, nephropathy, and retinopathy) and macrovascular complications (coronary artery disease, peripheral vascular disease, and stroke). Lowering hemoglobin A1c (HbA1c) to less than or about 7% has shown a reduction in diabetic microvascular complications and if initiated shortly after diagnosis is associated with reduction in macrovascular disease.[4]

Recently, a new class of glucose-lowering drugs, known as sodium-glucose co-transporter 2 (SGLT2) inhibitors, have been under clinical development.[5] On March 29th 2013, the FDA approved Invokana® (Janssen Pharmaceuticals, Inc.), the first-in-class SGLT2 inhibitor for the treatment of type 2 diabetes in the United States.[6] This article will review this new agent including its pharmacology, pharmacokinetics, safety, efficacy and dosing.

Pharmacology and Pharmacokinetics

The sodium-glucose co-transporters, which reabsorb glucose in the kidneys, are a novel drug target and therapeutic strategy for type 2 diabetes. The kidneys play a pivotal role in glucose homeostasis by filtering and reabsorbing glucose in the blood. Typically, about 180 grams of glucose per day are filtered and reabsorbed by the kidneys, with less than 1% excreted into the urine. The SGLT2 subtype is responsible for 90% of reabsorbed glucose and is almost exclusively expressed in the S1 segment of the proximal convoluted tubules of the kidneys.[5]

When plasma glucose increases beyond a concentration threshold, between 200 and 250 mg/dL, the renal tubules capacity for glucose reabsorption is exceeded and glucose begins to be excreted in the urine.[5] In Phase I studies, dose-dependent decreases in the renal threshold for glucose excretion (RT_G) were observed with maximal suppression of RT_G to 80 mg/dL using the 300mg canagliflozin dose.[7,8] By inhibiting the SGLT2 co-transporters the reabsorption of glucose is prevented and glucose is excreted into the urine. Increasing urinary glucose excretion, by lowering the renal threshold for glucose (RT_G), is a new approach to reducing blood glucose levels.[5]

The oral bioavailability of canagliflozin is approximately 65%. While there are no meal-time restrictions, it is recommended that canagliflozin be taken before the first meal of the day in order to reduce postprandial glucose levels. The peak plasma concentrations increase in a dose-proportional manner and occur within 1 to 2 hours after oral administration. Canagliflozin has a large volume of distribution in healthy subjects (119 L) and extensively binds to plasma proteins (99%).[8]

The major metabolic elimination pathway for canagliflozin is O-glucuronidation by uridine diphosphate glucuronosyltransferase 1A9 (UGT1A9) and UGT2B4 to two inactive O-glucuronide metabolites. Only about 7% of canagliflozin is metabolized by cytochrome P450 3A4 (CYP3A4.) After administration of a single radioactive-labeled canagliflozin dose, 41.5%, 7.0% and 3.2% of the dose was recovered in the feces as unchanged canagliflozin, a hydroxylated metabolite and an O-glucuronide metabolite, respectively. About 33% of the dose was excreted into the urine, predominantly (30.5%) as O-glucuronide metabolites. The terminal half-life was 10.6 and 13.1 hours for the 100 and 300 mg doses, respectively. [8]

Notable drug interactions include UGT inducers and digoxin. In UGT inducers, such as rifampin, consider increasing the dose from the 100 to 300mg once a day. For patients on concomitant digoxin therapy, it is recommended to monitor for increased digoxin levels.[8]

Table 1: Summary of Phase 3 Clinical Trials used for FDA Approval [9-17]

Study (N)	N	Design	Arm (core study)	LS mean Change in HbA1c from BL* [%]
Monotherapy				
DIA3005 (Stenlof et al[9]) Add-on to diet and exercise	584	Main Study: 26-wk PC core + 26-wk AC (SITA) extension	PBO	+0.14
			CANA 100mg	-0.77 (-0.91[a])
			CANA 300mg	-1.03 (-1.17[a])
		High Glycemic Cohort: 26-wk (non-controlled)	CANA 100mg	-2.13
			CANA 300mg	-2.56
Dual Therapy				
DIA3006[10] (unpublished) Add-on to MET vs SITA + PBO	1284	26-wk 4-arm PC core + 26-wk AC (SITA) extension	PBO	N/A
			SITA 100mg	
			CANA 100mg	
			CANA 300mg	
DIA3009 (Cefalu et al[11]) Add-on to MET vs GLIM	1450	52-wk AC (GLIM) core + 52-wk AC (GLIM) extension	GLIM (uptitrated)	-0.81
			CANA 100mg	-0.82[e]
			CANA 300mg	-0.93[d]
Triple Therapy				
DIA3002 (Wilding et al[12]) Add-on to MET + GLIM vs PBO	469	26-wk PC core + 26-wk PC extension	PBO	-0.13
			CANA 100mg	-0.85 (-0.71[a])
			CANA 300mg	-1.06 (-0.92[a])
DIA3012 (Forst et al[13]) Add-on to MET + PIO vs PBO	342	26-wk PC core + 26-wk AC (SITA) extension	PBO	-0.26
			CANA 100mg	-0.89 (-0.62[a])
			CANA 300mg	-1.03 (-0.76[a])
DIA3015 (Schernthaner et al[14]) Add-on to MET + GLIM vs SITA	755	26-wk AC (SITA)	SITA 100mg	-0.66
			CANA 300mg	-1.03[e]
Combination Therapy with Insulin ± AHAs				
DIA3008 (Matthews et al[15]) Add-on to insulin ± AHAs vs PBO	1718	18-wk PC	PBO	+0.01
			CANA 100mg	-0.63 (-0.65[a])
			CANA 300mg	-0.72 (-0.73[a])
Special Populations				
DIA3004 (Yale et al[16]) Moderate Renal Impairment	269	26-wk PC core + 26-wk PC extension	PBO	-0.03
			CANA 100mg	-0.33 (-0.30[d])
			CANA 300mg	-0.44 (-0.40[a])
DIA3010 (Bode et al[17]) Older patients (55 to 80 years)	714	26-wk PC core + 26-wk PC extension	PBO	-0.03
			CANA 100mg	-0.60 (-0.57[a])
			CANA 300mg	-0.73 (-0.70[a])

*=Least squares mean change in HbA1c from baseline to end of core study period (difference vs comparator); a= p<0.001 difference vs comparator; b= p<0.01 difference vs comparator; c= p<0.05 difference vs comparator; d=superior to comparator (upper limit of 95% CI less than pre-specified margin of 0.0%); e= non-inferior to comparator (upper limit of 95% CI less than pre-specified margin of 0.3%); f= not significant vs comparator; g= statistical comparison not performed;
Abbreviations: AC = active-controlled; AHA=antihyperglycemic agent; BL=baseline; CANA=canagliflozin; HbA1c= hemoglobin A1C; LS=least squares; MET=metformin; N/A = not available; PIO=pioglitazone; PBO=placebo; PC = Placebo-controlled; SITA=sitagliptin; wk=week

Table 2: Select Phase 3 Clinical Trial Endpoints[9-17]

Study	Arm (core study)	HbA1c<7% [%]*	FPG [mg/dL]*	Weight [%]*	Hypoglycemia [%]
Monotherapy					
DIA3005 (Stenlof et al[9]) Add-on to diet and exercise Main Study	PBO	20.6	+9	-0.6	2.6
	CANA 100mg	44.5 (23.9[a])	-27 (-36[a])	-2.8 (-2.2[a])	3.6[g]
	CANA 300mg	62.5 (41.9[a])	-34.2 (-43.2[a])	-3.9 (-3.3[a])	3.0[g]
High Glycemic Cohort	CANA 100mg	17.4	-81	-3.0	N/A
	CANA 300mg	11.6	86.4	-3.8	N/A
Dual Therapy					
DIA3006[10] (unpublished) Add-on to MET vs SITA + PBO	-	NA	NA	NA	NA
DIA3009 (Cefalu et al[11]) Add-on to MET vs GLIM	GLIM (uptitrated)	55.8	-18.3	+1.0	34.2
	CANA 100mg	53.6[g]	-24.3[g]	-4.2 (-5.2[a])	5.6 (-28.6[a])
	CANA 300mg	60.1[g]	-27.5[g]	-4.7 (-5.7[a])	4.9 (-29.3[a])
Triple Therapy					
DIA3002 (Wilding et al[12]) Add-on to MET + GLIM vs PBO	PBO	18.0	+4.1	-0.7	15.4
	CANA 100mg	43.2 (25.2[a])	-18.2 (22.3[a])	-2.1 (-1.4[a])	26.8[g]
	CANA 300mg	56.6 (38.6[a])	-30.5 (34.6[a])	-2.6 (2.0[a])	30.1[g]
DIA3012 (Forst et al[13]) Add-on to MET + PIO vs PBO	PBO	32.5	+2.52	-0.1	2.6
	CANA 100mg	46.9 (14.4[b])	-26.8 (-29.3[a])	-2.8 (-2.7[a])	2.7[g]
	CANA 300mg	64.3 (31.8[b])	-33.1 (-35.6[a])	-3.8 (-3.7[a])	5.3[g]
DIA3015 (Schernthaner et al[14]) Add-on to MET + GLIM vs SITA	SITA 100mg	35.3	-5.4	+0.3	40.7
	CANA 300mg	47.6[g]	-30.6 (-25.2[a])	-2.5 (-2.8[a])	43.2[g]
Combination Therapy with Insulin +/- AHAs					
DIA3008 (Matthews et al[15]) Add-on to insulin ± AHAs vs PBO	PBO	7.7	+3.6	+0.1	36.8
	CANA 100mg	19.8 (12.1[a])	-18.0 (-23.4[a])	-1.8 (-1.9[a])	49.3[g]
	CANA 300mg	24.7 (17[a])	-25.2 (-28.8[a])	-2.3 (-2.4[a])	48.6[g]
Special Populations					
DIA3004 (Yale et al[16]) Moderate Renal Impairment	PBO	17.2	+0.5	+0.3	52.9
	CANA 100mg	27.3[g]	-14.9[g]	-1.2[g]	51.2[g]
	CANA 300mg	32.6[g]	-11.7[f]	-1.5[g]	36.4[g]
DIA3010 (Bode et al[17]) Older patients (55 to 80 years)	PBO	28.0	+7.2	-0.1	28.7
	CANA 100mg	47.7 (19.7[a])	-18.1 (-25.5[a])	-2.4 (-2.3[a])	33.5[g]
	CANA 300mg	58.5 (30.5[a])	-20.3 (-33.2[a])	-3.1 (-3.1[a])	36.3[g]

*=least squares mean change from baseline to end of core study period (difference vs comparison); a= p<0.001 diference vs comparator; b= p<0.01 difference vs comparator; c= p<0.05 difference vs comparator; d=superior to comparator (upper limit of 95% CI less than pre-specficied margin of 0.0%); e= non-inferior to comparator (upper limit of 95% CI less than pre-specified margin of 0.3%); f= not significant vs comparator;
AHA=antihyperglycemics; CANA=canagliflozin; GLIM=glimepiride; HbA1c=hemoglobin A1c; FPG=fasting plasma glucose; g= statistical comparison not performed;LSM=least squares mean; PBO=placebo; PG=plasma glucose; PIO=pioglitazone; SBP=systolic blood pressure; SITA=sitagliptin

Clinical Trials

The safety and efficacy of canagliflozin was evaluated in 10,285 patients in nine randomized, double-blind clinical trials.[9-17] Seven studies were placebo-controlled[9,10,12,14-17] and two studies were active-controlled[11,13]. It was studied as monotherapy, as part of dual therapy, as part of triple therapy and as part of multiple therapy in combination with insulin with or without other antihyperglycemic agents.[9-17] In the active-controlled studies, canagliflozin was compared head-to-head with two second-line agents, sitagliptin and glimepiride.[10,11] Canagliflozin was also evaluated in two specific populations: older patients and patients with moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥30 and <50mL/min/1.73m^2).[16,17]

Study populations included adult patients with type 2 diabetes aged either 18 to 80 years old[9-12] or 18 years and older[13-15], with the exception of the studies in specific populations. The study evaluating older patients and patients with moderate renal impairment were aged 55 to 80 years old and at least 25 years old, respectively.[16,17] To be eligible for studies, the baseline hemoglobin A1c (HbA1c) of subjects had to be within a pre-specified range. The range for most studies was ≥7% to <10.5%.[10,12-15,17] Other studies included patients with a baseline HbA1c of ≥7% to <9.5%[11] and ≥7% to <10%.[9,17]

The primary efficacy endpoint for all studies was change in HbA1c from baseline. In all phase 3 trials, canagliflozin demonstrated a reduction in HbA1c from baseline **(Table 1)**. Secondary endpoints varied among studies but included percentage of subjects achieving HbA1c ≥7% and changes from baseline in fasting plasma glucose (FPG), body weight, systolic blood pressure (SBP) and fasting lipids. In most studies, canagliflozin demonstrated reductions from baseline in FPG, body weight and SBP but was also associated with increases in low-density lipoprotein (LDL) **(Table 2)**.[9-17]

There is an ongoing phase 3 study, Canagliflozin Cardiovascular Assessment Study (CANVAS), assessing cardiovascular risk (CV) for major adverse cardiac events in patients who have a history of CV events or have a high risk for CV events.[15] The FDA is also requiring four other post-marketing studies: two pediatric studies under the Pediatric Research Equity Act (PREA), a bone safety study, and a pharmacovigilance program to monitor for malignancies.

Monotherapy

Over the 26 week study period, canagliflozin 100mg and 300mg as add-on to diet and exercise met the primary efficacy endpoint, significantly reducing HbA1c by -0.77% and -1.03% respectively compared to a +0.14% increase in HbA1c with placebo (p<0.001 for both doses compared to placebo). At 26 weeks, canagliflozin 100mg and 300mg also significantly improved 2-hour post-prandial glucose levels (least squares (LS) mean difference from placebo -48.6mg/dL and -64.8mg/dL respectively, p<0.001 for both doses compared to placebo). The incidence of hypoglycemia was similar with canagliflozin 100mg and 300mg compared to placebo (3.6%, 3.0% and 2.6%, respectively). Significant reductions in body weight, FPG and SBP were also observed at the end of the study period (p<0.001 for comparisons to placebo for both doses).[9]

Dual Therapy

Canagliflozin 300mg as add-on to metformin demonstrated a greater HbA1c reduction compared to glimepiride (uptitrated to 6 to 8mg daily depending on country-specific maximum dosage) from baseline to 52 weeks (LS mean difference -0.12%, 95% CI: -0.22% to -0.02%). Both canagliflozin 100mg and 300mg significantly reduced body weight compared to an increase with glimepiride (-5.2%, -5.7% and +1.0%, respectively, p<0.001 for both doses). Canagliflozin 100mg and 300mg had a lower incidence of hypoglycemia compared to glimepiride (5.6%, 4.9% and 34.2%, respectively). Secondary endpoints also showed numerical improvements in SBP and HDL over the study period.[11]

Triple Therapy

Canagliflozin 100mg and 300mg as add-on to metformin and glimepiride significantly reduced HbA1c compared to placebo at 26 weeks (LS mean difference -0.71% and -0.92% respectively, p<0.001 for both doses). Canagliflozin 100mg and 300mg also significantly reduced FPG at 26 weeks compared to an increase with placebo (-18.2%, -30.5% and +4.1%, respectively, p<0.001 for both doses.) The incidence of hypoglycemia was numerically greater in the canagliflozin 100mg and 300mg groups compared to placebo (26.8%, 30.1% and 15.4%, respectively).[12]

Canagliflozin 300mg as add-on to metformin and glimepiride demonstrated non-inferiority to sitagliptin 100mg once daily in reducing HbA1c from baseline over 52 weeks (-1.03% and -0.66%, respectively). In the same study, canagliflozin 300mg had a greater reduction in FPG (-30.6 versus -5.4 mg/dL, p<0.001). Significantly greater reductions in body weight and SBP were also observed (p<0.001 compared to sitagliptin).[14]

Canagliflozin 100mg and 300mg as add-on to metformin and pioglitazone (30 or 45mg once daily) significantly reduced HbA1c over 26 weeks compared

to placebo (LS mean difference -0.62% and -0.76% respectively, p<0.001 for both doses). In the same study, canagliflozin 100mg and 300mg significantly lowered FPG at 26 weeks compared to an increase in FPG in the placebo group (-26.8, -33.1 and +2.52 mg/dL respectively, p<0.001). However, at 26 weeks HDL levels were significantly greater in the canagliflozin 100mg and 300mg groups compared to placebo (+7.1%, +11.3% and -0.4%, respectively, p<0.001).[13]

Combination Therapy with Insulin

Canagliflozin 100mg and 300mg as add-on to insulin with or without other antihyperglycemic agents significantly reduced HbA1c at 18 weeks compared to an increase observed in the placebo group (-1.9, -2.4 and +0.1%, respectively, p<0.001). Similarly, canagliflozin 100mg and 300mg significantly reduced FPG from baseline compared to an increase with placebo (-18.0, -25.2 and +3.6 mg/dL, respectively, p<0.001). Significant reductions in body weight were also observed at 18 weeks in the canagliflozin 100mg and 300mg groups relative to an increase in body weight in the placebo group (-1.9%, -2.4% and +0.1%, respectively). However, a greater incidence of hypoglycemia occurred in the canagliflozin 100mg and 300mg groups compared to placebo (49.3%, 48.6% and 36.8%, respectively).[15]

Moderate Renal Impairment

In a population of patients with decreased renal function (eGFR ≥30 and <50mL/min/1.73m^2), canagliflozin 100mg and 300mg significantly reduced HbA1c from baseline over 26 weeks compared to placebo (-0.03, -0.30, and -0.44%, respectively, p<0.001 for both doses). Both canagliflozin doses also demonstrated numerically greater improvements in body weight, FPG and SBP compared to placebo. Over the 26 -week study period, numerically greater reductions in eGFR from baseline were observed with canagliflozin 100mg and 300mg compared to placebo, with least square mean changes of -3.6, -3.9 and -1.4 mL/min/1.73m^2, respectively. Using the urine albumin/creatinine ratio (ACR) as an indicator, no evidence of renal injury with canagliflozin treatment was suggested. Canagliflozin 100mg and 300mg demonstrated greater numerical reductions in ACR at 26 weeks compared to placebo, with median percent reductions of -29.9%, -20.9%, and -7.5%, respectively.[16]

Patients 55 to 80 years old

In this older population study, the use of canagliflozin was examined in patients on their current regimens, with 75.6% of patients on 2 or more glucose-lowering medications. Over 26 weeks, canagliflozin 100mg and 300mg showed significantly greater reductions in HbA1c compared to placebo (-0.60%, -0.73% and -0.03%, respectively, p<0.001 for both doses). Significant improvements in body weight, SBP, FPG and HDL were also observed over the study period. However, numerically greater increases in LDL were observed at 26 weeks relative to placebo (+14.2%, +14.5% and +6.7%, respectively). Overall both canagliflozin doses were well tolerated, which suggests that canagliflozin may be an appropriate treatment option for older patients in combination with other type 2 diabetic medications.[17]

Adverse Events

Overall, canagliflozin 100mg and 300mg were well tolerated. In data aggregated from four 26-week placebo-controlled trials in which patients were only on assigned monotherapy, dual therapy or triple therapy, the most common adverse reactions were genital mycotic infections, urinary tract infections, and increased urination **(Table 3)**. The incidence of adverse events was also examined in eight larger placebo- and active-controlled trials (including 6177 patients) in which patients were on a wide range of background antihyperglycemic therapies. The types and rates of common adverse events were similar to those noted in **Table 3**.[8]

SGLT2 inhibitors differ from most antihyperglycemic drugs in that they act independently of insulin.[5] In all clinical trials, hypoglycemia was defined as any glucose value equal to or below 70mg/dL.[8] In an analysis of phase 3 trials in patients not on insulin or glimepiride (i.e. the monotherapy study[9], the add-on to metformin study[10], and the add-on to metformin/pioglitazone study[13]), the incidence of hypoglycemic

Table 3: Adverse Reactions reported in ≥ 2% of Patients in Placebo-controlled Trials[8]

Adverse Reaction	Placebo (N=646)	canagliflozin 100mg (N=833)	canagliflozin 300mg (N=834)
Female genital mycotic Infections	3.20%	10.40%	11.40%
Urinary tract infections	4.00%	5.90%	4.30%
Increased Urination	0.80%	5.30%	4.60%
Male genital mycotic infections	0.60%	4.20%	3.70%
Vulvovaginal pruritus	0.00%	1.60%	3.00%
Thirst	0.20%	2.80%	2.30%
Constipation	0.90%	1.80%	2.30%
Nausea	1.50%	2.20%	2.30%

episodes overall was low. The incidence was higher in the canagliflozin 300mg groups and 100mg compared to placebo groups (4.3, 3.8 and 2.2%, respectively). This analyses suggests a low risk of hypoglycemia in patients treated with canagliflozin alone or in combination with agents not associated with hypoglycemia.[18] Conversely, an increased incidence of hypoglycemia was observed when canagliflozin was used in combination with insulin or glimepiride **(Table 2)**.[11,12,14-17] It is recommended to consider lowering the dose of insulin or insulin secretagogue when used concomitantly with canagliflozin.[8]

Canagliflozin induces osmotic diuresis, which can lead to intravascular volume depletion. Symptomatic hypotension may occur in patients with impaired renal function (eGFR<60 mL/min/1.73m2), elderly patients, patients with low systolic blood pressure or patients on diuretics, angiotensin-converting-enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs).[8]

Dosing and Administration

Canagliflozin is produced in 100 and 300mg tablets for oral administration. The recommended starting dose is 100mg once daily, to be taken before the first meal of the day. The dose may be increased to 300mg daily in patients who tolerate the 100mg dose and have adequate kidney function (eGFR of 60 mL/min/1.73m2 or greater). Do not initiate canagliflozin in patients with an eGFR of 45 mL/min/1.73m2 or less.[8]

Cost

The average retail price obtained from an informal survey of three different chain pharmacies for a 30-day supply was $320.09 with prices ranging from $312.99 to $327.95. At this average monthly price, the average cost for a year supply without insurance is $3841.12.

Summary

Canagliflozin is the first FDA-approved SGLT2 inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.[6] Canagliflozin has been evaluated in 10,285 patients and has demonstrated clinically important and statistically significant improvements in glycemic control compared to placebo. These improvements were associated with weight loss and a low incidence of hypoglycemia. The recommended starting dose is 100mg once daily, to be taken before the first meal of the day.[8] Canagliflozin's novel mechanism of action, increasing urinary glucose excretion, represents a new approach to controlling hyperglycemia and provides type 2 diabetic patients with an additional treatment option.

References

1. Centers for Disease Control and Prevention. National Diabetes Fact Sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. (accessed 2013 April 8).
2. Centers for Disease Control and Prevention. Increasing Prevalence of Diagnosed Diabetes-United States and Puerto Rico, 2012. www.cdc.gov/diabetes/statistics. (accessed 2013 April 8.)
3. Prentki M, Nolan C. J. Islet Cell Failure in Type 2 Diabetes. J Clin Invest 2006; 116:1802–1812.
4. Inzucchi SE, Bergenstal RM, Buse JB et al. Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach. Diabetes Care 2012; 35:1364-1379.
5. Chao EC, Henry RR. SGLT2 Inhibition— a novel strategy for diabetes treatment. Nat Rev Drug Discov 2010; 9:551-9.
6. United States Food and Drug Administration. News & Events: FDA Approves Invokana to Treat Type 2 Diabetes. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm345848.htm. (accessed 2013 April 14)
7. Rosenstock J, Aggarwal N, Polidori D et al. Dose-Ranging Effects of Canagliflozin, a Sodium-Glucose Cotransporter 2 Inhibitor, as Add-On to Metformin in Subjects with Type 2 Diabetes. Diabetes Care 2012;35:1232-38.
8. Product Information. Invokana (canagliflozin). Package Insert: Prescribing Information. Titusville, NJ: Janssen, February 2013.
9. Stenlof K, Cefalu WT, Kim KA, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab. 2013; 15: 372-382.
10. United States National Institutes of Health. The CANTATA-D Trial (CANagliflozin Treatment and Trial Analysis - DPP-4 Inhibitor Comparator Trial. www.clinicaltrials.gov/ct2/show/NCT0110667 (accessed 2013 April 12)
11. Cefalu WT, Leiter LA, Niskanen L, et al. Efficacy and safety of a Sodium Glucose Co-Transporter 2 Inhibitor, Compared With Glimepiride in Patients with Type 2 Diabetes on Background Metformin. Presented at: 72nd Scientific Sessions of the American Diabetes Association (ADA), Philadelphia, PA, June 8-12 2012.
12. Wilding J, Mathieu C, Vercruysse, et al.

Canaglifozin, a Sodium Co-Transporter 2 Inhibitor, Improves Glycemic Control and Reduces Body Weight in Subjects With Type 2 Diabetes Inadequately Controlled With Metformin and Sulfonylurea. Presented at: 72nd Scientific Sessions of the American Diabetes Association (ADA), Philadelphia, PA, 2012 June 8-12.
13. Forst T, Guthrie R, Goldenberg, et al. Efficacy and Safety of Canagliflozin in Subjects With Type 2 Diabetes on Metformin and Pioglitazone. Presented at: 4th World Congress on Controversies to Concensus in Diabetes, Obesity and Hypertension (CODHy), Barcelona, Spain. 2012, November 8-11.
14. Schernthaner G, Gross JL, Rosenstock J, et al. Canagliflozin Compared With Sitagliptin for Patients With Type 2 Diabetes Who Do Not Have Adequate Glycemic Control With Metformin Plus Sulfonylurea: A 52-week randomized trial. Diabetes Care. Epub 5 Apr 2013. DOI 10.2337/dc12-2491
15. Matthews D, Fulcher G, Perkovic V, et al. Efficacy and Safety of Canagliflozin, an Inhibitor of Sodium Glucose Co-Transporter 2, Added On to Insulin Therapy With or Without Oral Agents in Type 2 Diabetes. Presented at: 48TH Annual Meeting of the European Association for the Study of Diabetes (EASD), Berlin, Germany. 2012, October 1-5.
16. Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab. 2013; 15: 463–473.
17. Bode B, Stenlof K, Sullivan D, et al. Efficacy and Safety of Canagliflozin Treatment in Older Subjects with Type 2 Diabetes Mellitus: A Randomized Trial. Hospital Practice 2013;41:72-84.
18. Canagliflozin as an Adjunctive Treatment to Diet and Exercise Alone or Co-administered with Other Antihyperglycemic Agents to Improve Glycemic Control in Adults with Type 2 Diabetes Mellitus. Presented at: FDA Endocrinologic and Metabolic Drugs Advisory Committee Meeting. Silver Spring, MD, January 10, 2013.

Clinical Trial Update

Agnelli G et al. Oral Apixaban for the Treatment of Acute Venous Thromboembolism. N Engl J Med. 2013 Jul 1 — Apixaban is an oral factor Xa inhibitor that has been approved for stroke prevention in patients with non-valvular atrial fibrillation. AMPLIFY was a randomized, double-blind trial that compared apixaban to conventional therapy for patients with acute venous thromboembolism (VTE).

Experimental Group: Apixaban 10 mg twice daily for 7 days, followed by apixaban 5 mg twice daily for 6 months. **Control Group:** Enoxaparin 1 mg/kg every 12 hours for at least 5 days and warfarin initiated concurrently and dose adjusted to an INR of 2.0 to 3.0. Enoxaparin was discontinued when INR was ≥ 2.0.

Inclusion: Age ≥ 18 years, confirmed and symptomatic proximal DVT or PE. **Exclusion:** High risk for or active bleeding, contraindication for warfarin or enoxaparin, cancer with long term LMWH therapy plan, provoked VTE without persistent risk factor for recurrence, less than 6 months of therapy planned, another indication for anticoagulation, dual antiplatelet therapy, aspirin use at dose > 165 mg daily, concurrent use of potent CYP 3A4 inhibitors, serum creatinine level of more than 2.5 mg per deciliter, or creatinine clearance of less than 25 mL per minute. (See article for additional criteria)

Results were analyzed for intention-to treat. Apixaban was found to be noninferior to conventional therapy with regard to the primary outcome which was the composite of recurrent symptomatic VTE or death related to VTE, 2.3% vs. 2.7%, $p < 0.001$ for noninferiority. The incidence of major bleeding was less in the apixaban group, 0.6% vs. 1.8%, $p < 0.001$ for superiority.

This study showed that apixaban alone was as effective for acute VTE as conventional therapy with less risk for major bleeding. Additional information is needed for some patient groups, including those with cancer, body weight less than 60 kg, or creatinine clearance less that 50 mL per minute.

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