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Brexafemme® (ibrexafungerp): A Novel Drug to Knock Out Vulvovaginal Candidiasis

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Vulvovaginal candidiasis (VVC) is a common fungal infection that affects millions of women yearly and is most commonly caused by *Candida albicans*.[1] In 2014, more than a third of outpatient visits concerning non-invasive candidiasis were due to VVC, totaling almost $370 million in direct medical costs.[2] Although the estimated cost of a visit was relatively low ($186-$287), the burden of VVC should not be ignored as it greatly affects public health. Even though some species of *Candida* grow on humans as a part of their normal flora, the fungus can overgrow and become a burden if the microbiome is altered.[1] The environment can be changed from recent antibiotic use, spermicides, or douching. *Lactobacillus* normally protects the vagina from *Candida* species, but it can be removed by the previously mentioned methods.

Most VVC cases are mild and include symptoms such as dysuria, thick vaginal discharge, and vulvar edema and pruritus.[3] However, cases can be classified as severe if they meet one of the following criteria: the infection is caused by a *Candida* species other than *albicans*; the patient has comorbidities that increase the risk of VVC, such as uncontrolled diabetes or immunosuppression; or the infection is a recurrent episode, defined as four episodes of VVC within one year.[4] Women who are more likely to develop a vaginal infection include those who are pregnant, use birth control, wear tight clothing, or have poor personal hygiene.

To treat uncomplicated VVC, fluconazole or topical agents such as intravaginal suppositories of boric acid or nystatin are strongly recommended by the Infectious Diseases Society of America (IDSA) 2016 guidelines.[5] Topical antifungals such as miconazole and clotrimazole work the same way as fluconazole, but are unlikely to cause systemic side effects since they work locally on the infection.[7] Although fluconazole is preferred by most patients as it is currently the only oral pill option, it may not be effective against all Candida species. Fluconazole-resistant strains have been recently documented, with resistance likely related to long-term use of fluconazole when treating recurrent VVC.[8] In a trial by Zhang et al., the susceptibility rate of *C. albicans* to fluconazole was 88.3%, dose-dependent susceptibility was 7.0%, and resistance was 4.7% of the study population.[9] Other *Candida* species such as *galbrata* and *krusei* had increased intrinsic resistance to fluconazole. This azole resistance is due to efflux pumps, specifically the overexpressed CDR1 gene.

Announced by Scynexis in June 2021, Brexafemme® (ibrexafungerp) serves as the first non-azole oral treatment for VVC and is planned to launch later in 2021.[10] As a triterpenoid antifungal, it has proven effective against azole-resistant strains of *Candida* and other fungi such as *Aspergillus*.[11] Ibrexafungerp increases its appeal with its one-day dose regimen, similar to fluconazole, to treat VVC: two 150 mg tablets are taken in the morning and two more at night for a total dose of 600 mg.[10] This article will review the trials giving ibrexafungerp FDA approval and synthesize its medicinal properties and implications in VVC therapy.

Pharmacology

Mechanism of Action

Ibrexafungerp is a concentration-dependent fungicidal antimicrobe against *Candida* species and is fungistatic against *Aspergillus* species.[12] Ibrexafungerp is a triterpenoid antifungal that inhibits glucan synthase which is involved in the formation of 1,3-β-D-glucan.[10] This component is essential to creating the fungal cell wall. Additionally, ibrexafungerp maintains activity at pH 4.5, which is crucial for its activity in the normally acidic vagina.[10]

Ibrexafungerp remains active against most fluconazole-resistant *Candida* species; however, there is concern for potential resistance in FKS gene mutations as these genes encode the catalytic site of 1,3-β-D-glucan synthase.[12] This speculation is due to FKS mutations. These mutations can create resistance to echinocandins, another group of antifungals. According to a study by Pham et al., 81% of echinocandin-resistant isolates had an FKS mutation.[13] Most mutations causing resistance to ibrexafungerp are located within the *FKS2* gene.

Pharmacokinetics

Ibrexafungerp reaches maximum concentrations in the plasma approximately 4-6 hours after oral administration.[10] The area under the curve (AUC) and maximum concentration (C_{max}) are increased by roughly 35% when ibrexafungerp is taken with a high-fat meal. However, this increase is not considered to be clinically

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significant, so ibrexafungerp can be taken with or without food. The mean steady state volume of distribution (V_{ss}) is about 600 L with tremendous binding to protein at greater than 99%. Animal models have uncovered a 9-fold higher exposure of ibrexafungerp in vaginal tissue than in blood, but this has yet to be shown in human studies.[10]

Ibrexafungerp is hydrolyzed by CYP3A4 and is then further glucuronidated and sulfated to become an inactive metabolite.[10] This medication is mostly eliminated via CYP3A4 metabolism and biliary excretion. The elimination half-life ($T_{1/2}$) is roughly 20 hours, with an average of 90% of the oral dose recovered in feces (51% as unmetabolized ibrexafungerp) and 1% found in urine. The remaining 9% has not been accounted for.[10] Key pharmacokinetic parameters are summarized in **Table 1**.

Table 1 | Select Ibrexfungerp Pharmacokinetics[10]

Absorption	
T_{max}[a]	4-6 hours
Distribution	
V_{ss}[b]	600 L
Protein Binding	>99%
Metabolism	
	CYP3A4
Elimination	
$T_{1/2}$[c]	20 hours
Fecal	90%
Urine	1%

[a]Time to maximum concentration; [b]Steady state volume of distribution; [c]Half-life

Clinical Trials

FDA approval of ibrexafungerp relied on data from two randomized control trials, VANISH 303 and VANISH 306.[10] This section will summarize those experiments as well as a trial directly comparing ibrexafungerp to fluconazole. Results from all trials discussed are collected in **Tables 2 and 3**.

VANISH 303 Trial[14]

As a phase 3 study sponsored by Scynexis, Inc., VANISH 303 examined the efficacy and safety of ibrexafungerp in patients with VVC against placebo in a randomized 2-to-1 ratio.[14] The multicenter double-blind trial took place in 25 different locations across the United States, and included 290 subjects (190 ibrexafungerp patients and 100 placebo patients) who were postmenarchal females at or above 12 years of age with symptomatic acute vulvovaginal candidiasis (AVVC). Diagnosis of AVVC was confirmed by two or more signs or symptoms of VCC (e.g., itching, edema, erythema, etc.), budding yeast or hyphae found via microscope, and vaginal pH of less than or equal to 4.5. Patients excluded from the study met one of the following criteria: had an infection from multiple causes, had a VVC in the past 28 days prior to trial randomization, were currently menstruating, had uncontrolled diabetes, or had previous or current cervical or vaginal cancer. The average age of the women in the study was 34 years old, ranging from 17-67 years old.[10] Both arms were similar with 54% Caucasians, 40% African Americans, and 26% Latinos or Hispanics.

The intervention therapies entailed ibrexafungerp 300 mg by mouth every 12 hours for one day or matching placebo.[14] The primary outcome measure was the percentage of patients who had elimination of signs and symptoms of VVC at the test-of-cure (TOC) visit which happened between Days 8 to 14 after drug administration. Secondary outcomes included mycological eradication at the TOC visit, percentage of patients with both clinical cure and negative cultures at TOC visit, complete resolution of symptoms at day 25 after intervention, and the number of subjects with adverse effects due to treatment within 29 days of treatment. The study did not discuss if patients were allowed to treat their symptoms due to ineffective therapy.[10,14]

Of note, over 90% of the cultures were positive with *Candida albicans*, the most common cause of VVC.[1,10] However, no data concerning the other *Candida* species were discussed, such as the species collected and the efficacy of ibrexafungerp against these isolates.[10,14] With respect to the study's primary outcome, 95 patients treated with ibrexafungerp (50.0%) had no signs or symptoms of infection at the TOC visit compared to 28 patients in the placebo group (28.0%), p-value=0.001. Those who had negative cultures at the TOC encounter were 94 patients (49.5%) in the ibrexafungerp arm and 19 patients (19.0%) in the placebo arm (p-value <0.001). On day 25, the ibrexafungerp group had 113 patients (59.5%) with complete elimination of signs and symptoms of infection versus placebo which had 44 patients (44.0%), p-value=0.007. All primary and secondary outcomes can be found in **Tables 2 and 3.**

VANISH 306 Trial[15]

This randomized phase 3 trial evaluated the efficacy and safety of ibrexafungerp compared to placebo in the setting of AVVC in females at least 12 years old that have had at least one menstruation in their lifetime, similar to the VANISH 303 study.[15] Unlike VANISH 303, this multicenter and double-blinded experiment branched outside of the United States with 61% of the study population in Bulgaria and 39% in the United States.[10,14-15] The 366 subjects were randomized to ibrexafungerp or matching placebo in a 2-to-1 ratio (189 and 89 patients, respectively).[10,15] Patients were given either ibrexafungerp or placebo for one day and were followed for one month after administration was completed.[15] Most aspects of the study design mimicked the VANISH 303 trial, including intervention arms (ibrexafungerp 300 mg twice daily for one day or matching placebo), inclusion and exclusion criteria, and primary and secondary outcome measures. This trial was also sponsored by the drug manufacturer. Of note, the menstruation at the baseline visits exclusion criterion from VANISH 303 was not a part of this study's design.[14,15]

The average age of patient population was 34 years old, with a range of 18-65 years old.[10] Like VANISH 303, most participants (92%) in this trial were less than 50 years old. This study was comprised of mainly Caucasians (81%) with 19% African Americans and 10% Hispanics or Latinos. Five percent (5%) of the participants had a history of diabetes and the mean BMI was 26. *Candida albicans* was found on 89% of the cultures at the time of randomization.

For the primary outcome measure, 120 ibrexafungerp patients (63.5%) had no symptoms of VVC compared to 40 placebo patients (44.9%) at the TOC visit which occurred between Days 8

and 14 after treatment (p-value=0.009). Concerning the two secondary outcome measures, 111 ibrexafungerp subjects (58.7%) had negative cultures during the same TOC visit as opposed to 26 people (29.2%) in the placebo arm (p-value <0.001), and 137 ibrexafungerp participants (72.5%) achieved complete clinical response while only 44 placebo patients (49.4%) had full resolution of their symptoms at the final follow-up visit (p-value= 0.006). Primary and secondary outcomes from these studies can be reviewed in **Tables 2 and 3**.

DOVE Trial[16]

Although this trial was not considered for the approval of ibrexafungerp, it is important to include here as it tests the novel drug against an active comparator, fluconazole.[6,10] This double-blinded, double-dummy study was completed at 25 locations across the United States.[16] This trial had nearly identical inclusion and exclusion criteria to VANISH 303, except that patients had to be 18 years or older to be eligible.[14,16] Like the two VANISH studies, the DOVE trial was solely sponsored by Scynexis, Inc. Despite its numerous similarities to the previous trials, DOVE is unique as it had multiple ibrexafungerp arms with different dosing regimens, driving the focus towards drug tolerability and efficacy.[16] Roughly 180 patients were equally randomized to one of six treatments (about 30 patients in each group) which consisted of one fluconazole arm (150 mg for one day) and five ibrexafungerp arms. The different ibrexafungerp regimens are as follows: 750 mg once for one day, 300 mg twice for one day, 450 mg twice for one day, 150 mg twice daily for three days, and 300 mg twice daily for three days. Like the VANISH trials, the primary outcome measure was resolution of signs and symptoms of AVVC at the TOC visit (between days 8-12 after treatment).[14-16] The secondary outcome measures included negative cultures and the number of adverse effects related to treatment by day 29 after administration. At the time of compiling this review, the DOVE results are not published in full. Information was collected only through the abstract available, which greatly limits accessible data. Statistics only concerning the ibrexafungerp 300 mg twice for one day arm were noted against the fluconazole arm. Investigators determined this aforementioned dose as the best possible balance between drug efficacy and tolerability.[16,17] For the primary outcome measure, 14 ibrexafungerp patients (52%) achieved symptom elimination versus 14 fluconazole patients (58%) at the TOC visit.[17] No statistics are available. As for the secondary outcome measures, 70% of ibrexafungerp patients had a clinical cure rate at day 25 while only 50% of fluconazole participants achieved resolution of infection symptoms.[17] At day 25, no ibrexafungerp patients exhibited signs or symptoms of infection while 47% of fluconazole patients had at least three or more unresolved symptoms. The primary and secondary outcomes from all studies are assembled in **Tables 2 and 3.**

Adverse Effects and Precautions

The most common adverse reactions seen with ibrexafungerp use compared to placebo included diarrhea (16.7% vs. 3.3%), nausea (11.9% vs. 4.0%), and abdominal pain (11.4% vs. 5.1%).[10] Dizziness (3.3% vs. 2.5%) and vomiting (2.0% vs. 0.7%) were also experienced by some patients. Additional side effects noted were dysmenorrhea, flatulence, back pain, elevated transaminases, vaginal bleeding, and a rash or hypersensitivity reaction (**Table 4**).[10] These adverse effects occurred in less than 2% of patients in both VANISH trials. Of note, one patient stopped ibrexafungerp treatment due to vomiting and another patient quit therapy because of associated dizziness.[10]

Dosage and Administration

Ibrexafungerp is approved in post-menarchal children and adults with VVC as 300 mg (two 150 mg tablets) administered every twelve hours for one day, for a total daily dose of 600 mg (four 150 mg tablets).[10] Doses can be taken with or without food. If the patient is currently taking a strong CYP3A4 inhibitor such as diltiazem or erythromycin, the dose should be decreased to 150 mg taken twice for one day. Discussion of whether the dose should be repeated if VVC remains symptomatic has not yet occurred.[10,14-17] Thus, clinical judgement should be utilized when deciding on a treatment regimen for a patient currently taking a strong CYP3A4 inhibitor.

Table 2 | Primary Outcomes from Ibrexafungerp Trials[10,14-17]

Trial	Outcome	Intervention	Result (95% CI)	P-Value
VANISH 303	Complete Clinical Response at TOC[a]	Ibrexafungerp 300mg BID[b]	50% (10.2)	0.001
		Placebo BID[b]	28% (32.8)	
VANISH 306		Ibrexafungerp 300mg BID[b]	63.5% (6.0)	0.009
		Placebo BID[b]	44.9% (30.6)	
DOVE		Ibrexafungerp 300mg BID[b]	52% (n/a[c])	n/a[c]
		Fluconazole 150mg once	58% (n/a[c])	

[a]Absence of signs and symptoms without the need for additional topical antifungal therapy for symptom relief at test of cure (TOC) visit at day 8-14 after end of treatment; [b]Twice a day; [c]Not available

Table 3 | Secondary Outcomes from Ibrexafungerp Trials[10,14-17]

Trial	Outcome	Intervention	Result (95% CI)	P-Value
VANISH 303	Negative Culture at TOC[a]	Ibrexafungerp 300mg BID[d]	49.5% (19.4)	<0.001
		Placebo BID[d]	19.0% (40.3)	
	Complete Clinical Response at Follow-up[b]	Ibrexafungerp 300mg BID[d]	59.5% (3.4)	0.007
		Placebo BID[d]	44.0% (27.1)	
VANISH 306	Negative Culture at TOC[a]	Ibrexafungerp 300mg BID[d]	58.7% (17.2)	<0.001
		Placebo BID[d]	29.2% (40.6)	
	Complete Clinical Response at Follow-up[b]	Ibrexafungerp 300mg BID[d]	72.5% (10.8)	0.006
		Placebo BID[d]	49.4% (35.0)	
DOVE	Negative Culture at TOC[a]	Ibrexafungerp 300mg BID[d]	70% (n/a[e])	n/a[e]
		Fluconazole 150mg once	50% (n/a[e])	
	Unresolved Infection Signs/ Symptoms[c]	Ibrexafungerp 300mg BID[d]	0% (n/a[e])	n/a[e]
		Fluconazole 150mg once	47% (n/a[e])	

[a]Absence of signs and symptoms without the need for additional topical antifungal therapy for symptom relief at test of cure (TOC) visit at day 8-14 after end of treatment; [b]Absence of signs and symptoms without the need for additional topical antifungal therapy for symptom relief at follow-up visit at day 25 after end of treatment; [c]Greater than 3 signs or symptoms of AVVC at day 25; [d]Twice a day; [e]Not available

Special populations

Renal & Hepatic Impairment

Ibrexafungerp has no dosage adjustments for those with decreased renal and hepatic functions.

Pregnancy & Lactation

Ibrexafungerp is contraindicated in pregnancy and those with hypersensitivity to the medication.[10] Interestingly, no trials discussed above deliberated on including or excluding pregnant patients from the study population.[14-16] The pregnancy concern is due to findings from animal studies as this antifungal may cause fetal harm.[10] Fetal malformations occurred at doses equal to or greater than five times the recommended human dose (RHD). Pregnancy should be confirmed to be negative in human patients before initiating ibrexafungerp therapy. Effective contraception should be stressed during ibrexafungerp treatment and four days after the administration of the last dose.[10]

There is currently no data on the presence of ibrexafungerp in human or animal breast milk.[10] Likewise, the effects of milk production or breast-feeding while taking this novel drug are unknown. The benefits and risks should be weighed.

Pediatric & Geriatric Patients

The safety and effectiveness of ibrexafungerp to treat VVC is established in post-menarchal pediatric females but use in pre-menarchal girls has not yet been evaluated.[10,14-15] No clinically significant pharmacokinetic differences were noted in geriatric patients compared to younger individuals in trials, but there is not enough data to determine with certainty that older patients will not respond differently. However, there is currently no dose adjustment based on age.[10]

Drug Interactions

Ibrexafungerp is a substrate of CYP3A4 and P-glycoprotein (P-gp, an efflux pump), and is an inhibitor of CYP2C8, CYP3A4, and P-gp and organic anion transporting polypeptide 1B3 (OATP1B3, an influx carrier) transporters.[10] CYP3A4 is not shown to be induced by ibrexafungerp. In patients taking strong CYP3A4 inhibitors such as verapamil or clarithromycin, the dose of ibrexafungerp should be decreased as concomitant administration of these medications can greatly increase the concentration of ibrexafungerp. The recommended dose in this situation is 150 mg by mouth taken every twelve hours for one day.[10] Mild and moderate CYP3A4 inhibitors do not increase ibrexafungerp concentrations enough to warrant dosing alterations.

In situations where strong or moderate CYP3A4 inducers such as rifampin or phenytoin are taken, ibrexafungerp administration is not recommended as this combination will significantly decrease the efficacy of ibrexafungerp.[10] Proton pump inhibitors (PPIs) like omeprazole can decrease ibrexafungerp concentrations, but not by a clinically significant amount that would require a dosing recommendation.[10] There are many enzymes that ibrexafungerp interacts with that do not require dosing adjustments. These include CYP2C8, CYP3A4, P-gp, and OATP1B3. All substrates of these enzymes have increased concentrations with coadministration of ibrexafungerp.[10]

Cost and Availability

Brexafemme® prices are currently ranging from $475 to $507 on GoodRx® for the full therapy course (4 tablets taken in one day).[18-19] Patients with insurance may be able to pay $30 for ibrexafungerp while those expecting to pay out-of-pocket are eligible to pay $120 for the treatment with a manufacturer savings card.[20] Even with this manufacturer coupon, ibrexafungerp is much more expensive than its competition, with fluconazole costing between $7 and $30 for most patients and topical antifungals like miconazole and clotrimazole being available over the counter (OTC) at prices ranging from $5 to $16.[21-23]

Clinical Implications

The VANISH 303 and VANISH 306 trials were crucial in FDA approval of ibrexafungerp.[10,14-15] Selection bias was greatly reduced due to double-blinding and randomization in both experiments. Ibrexafungerp was not compared against an active comparator in these studies which can limit the understanding of its true place in therapy.[5,10] The DOVE trial comparing fluconazole and ibrexafungerp should shed light on this debate, but due to the lack of concrete data published and the immense cost of ibrexafungerp, it is likely that fluconazole will remain the first-line treatment for VVC.[5,16-21] It is also interesting that the study designers included menstruation as an exclusion criterion for VANISH 303 and DOVE, as ibrexafungerp is an oral medication.[14,16] The reasoning behind this decision was not noted in either the trial details or the drug monograph.[10,14,16-17] Asian women were not included in either study, leaving a hole in the data as this group has a higher percentage of poor metabolizers for certain CYP pathways. Conflict of interest is possible in all three trials as the manufacturer, Scynexis, Inc., funded each study.[10,14-17]

Guidelines state the goal of VVC treatment is to cure the infection, making the primary and secondary outcome measures (complete clinical response and negative culture) of all three trials appropriate.[5,10,14-17] Ibrexafungerp did not have statistically significant data against placebo in the primary outcome measure of complete clinical response at the TOC visit in VANISH 306, while the opposite is true for VANISH 303.[10,14-15] Having conflicting data in nearly identical study designs does not support the efficacy of ibrexafungerp. Although in rare cases VVC can resolve on its own, most patients require treatment to cure the infection. Since many topical VVC treatments are available OTC, it is possible that some patients in both arms were self-treating to calm the symptoms they were experiencing, even though these studies required the absence of topical antifungal therapy.[10,14-16]

When comparing ibrexafungerp to fluconazole, the current standard of care, the former medication may be administered to patients who have contraindications to use of the latter or other traditional treatments. During pharmacodynamic safety testing, an ibrexafungerp concentration of five times greater than the recommended dose of 300 mg twice daily for one day was used and did not prolong the QTc interval.[10] Fluconazole is contraindicated in concomitant use with other QTc prolonging agents such as amiodarone, and is used cautiously in patients with bradycardia, heart failure, or electrolyte imbalances.[6] Although both fluconazole and ibrexafungerp are CYP3A4 inhibitors, ibrexafungerp did not affect the C_{max} of CYP3A4 substrate tacrolimus in studies; fluconazole is a moderate CYP3A4 inhibitor and often requires dose adjustments of CYP3A4 substrate concomitant medications.[6,10] Ibrexafungerp dosing should be halved (150 mg every 12 hours for one day) when administered with a strong CYP3A4 inhibitor, and an alternative therapy should be used when the patient is taking strong or moderate CYP3A4 inducers.[10] One advantage ibrexafungerp has over fluconazole regarding drug interactions is that the former does not interact with CYP2C9, while the latter is a potent inhibitor of the isoenzyme.[6,10] However, since VVC treatment with either fluconazole or ibrexafungerp will be a short course of therapy, it is unlikely that maintenance medications will need to be altered. It is possible that more drug interactions and dosing adjustments will be recommended once more real-world data is collected for ibrexafungerp.

Table 4 | Common Adverse Effects with Ibrexafungerp[10]

Adverse Effect	Incidence Rate
Diarrhea	16.7%
Nausea	11.9%
Abdominal Pain[a]	11.4%
Dizziness[b]	3.3%
Vomiting	2.0%

[a]Includes abdominal pain, upper and/or lower abdominal pain, and abdominal discomfort; [b]Includes dizziness and postural dizziness

Although ibrexafungerp may not be used for most VVC cases due to high cost, it may shine against fluconazole-resistant *Candida* species.[8-9] In addition, Scynexis, Inc., the manufacturer of ibrexafungerp, plans to submit a supplemental new drug application (NDA) to the FDA in the first half of 2022 for its use in preventing recurrent VVC.[24] The company also discusses expanding the novel drug's use to hospitals by treating life-threatening and invasive fungal infections via intravenous administration.

Conclusion

Brexafemme® (ibrexafungerp) is a triterpenoid antifungal approved for the treatment of VVC. This medication may cure VVC through symptom relief and fungal elimination after its one-day dosing regimen, but the trial data available is largely inconclusive. Ibrexafungerp appears to be both efficacious and safe in VVC treatment, while also limiting drug interactions. However, due to the lack of quality published data directly comparing fluconazole and ibrexafungerp, prescribers must weigh the benefits and risks of this new therapy along with using their clinical judgement to determine the best option for their patients.

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Drug Update:
New Indications and Dosage Forms
September 2021

Exkivity® (mobocertinib) Capsule
New Molecular Entity: First oral therapy indicated for treatment of metastatic NSCLC with epidermal growth factor receptor (EGFR) exon 20 mutation post platinum-based chemotherapy

Korsuva® (difelikefalin) Injection
New Molecular Entity: Kappa opioid receptor agonist used to treat moderate-to-severe itching associated with chronic kidney disease in adults undergoing hemodialysis

Kerendia® (finerenone) Tablet
New Formulation: Non-steroidal mineralocorticoid receptor antagonist (MRA) indicated to reduce risk of eGFR decline, end stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in patients with CKD associated with type 2 diabetes

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