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DEVELOPMENT OF EVOCALCET AS CALCIMIMETIC

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ABSTRACT
Evocalcet is a novel oral calcimimetic developed to overcome limitations of cinacalcet, such as gastrointestinal intolerance and CYP2D6-mediated drug interactions, while maintaining efficacy in suppressing parathyroid hormone (PTH) levels in secondary hyperparathyroidism (SHPT). In a 30-week randomized Phase III trial in Japanese hemodialysis patients, gastrointestinal adverse events occurred in 18.6% with evocalcet versus 32.8% with cinacalcet (difference −14.2% [95% CI −20.9, −7.5]), while PTH suppression met non-inferiority criteria (difference −4.0% [95% CI −11.4, 3.5]). Evocalcet demonstrated favorable pharmacokinetics with higher bioavailability (62–84%) and once-daily oral dosing. Limitations include restricted global availability and lack of long-term cardiovascular outcome data. This review summarizes the development, pharmacology, clinical evidence, and future directions of evocalcet.

KEYWORDS: Evocalcet, calcimimetic, calcium-sensing receptor, cinacalcet, dialysis, secondary hyper parathyroidism.

INTRODUCTION
Patients with chronic kidney disease (CKD), particularly those undergoing renal replacement therapy, may develop secondary hyperparathyroidism (SHPT), which is defined by elevated serum parathyroid hormone (PTH) levels. As CKD worsens, there is a sharp rise in Serum PTH levels raise serum calcium and phosphate levels and cause high turnover bone disease.[7] Vascular calcification, fractures, and an elevated risk of cardiovascular and all-cause death are frequently the outcomes of such aberrant mineral metabolism. Globally, the mean prevalence of CKD is almost 13%.[6] To preserve homeostasis, parathyroid hormone (PTH) regulates mineral metabolism in healthy people. The amount of extracellular ionized calcium (Ca2+) is the main factor regulating the release of PTH by parathyroid gland cells.[3] Physiological alterations brought on by declining renal function in CKD patients may contribute to abnormal mineral metabolism. These alterations include elevated blood phosphorus levels and decreased phosphorus excretion into the urine. The phosphorus buildup that results reduces the synthesis of active vitamin D and increases the synthesis and release of fibroblast growth factor.Ca2+and phosphorus homeostasis are disrupted as hyperparathyroidism Increased phosphorus and lowered levels of vitamin D and Ca2+ are among these alterations, which encourage the synthesis of hyper PTH secretion and parathyroid cell proliferation, which lead to secondary hyperparathyroidism (SHPT).[7]

Excessive quantities of PTH are secreted by larger parathyroid glands in patients with SHPT. Bone turnover is encouraged by persistently high PTH. It speeds up the release of calcium and phosphorus from bone, which can result in fractures, fibrous osteitis, and discomfort in the bones and joints.[6,7] Excessive release of calcium and phosphorus from bone can lead to ectopic calcification in the heart valves and blood vessels, which can increase morbidity.[1] In addition, immunological dysfunction, hypertension, anaemia, pruritis, sexual dysfunction, and other health issues are brought on by excessive PTH. It may also raise the risk of heart and vascular disease and mortality in these people.[8] Parathyroidectomy, which has been demonstrated to lower the risk of fracture, cardiovascular events, and mortality, may be necessary for patients with severe SHPT.[6] The calcium-sensing receptor (CaR), a G protein-coupled receptor on the cell surface, controls the release of PTH from parathyroid gland cells. The CaR's control on PTH secretion makes it a desirable therapeutic target for SHPT.[3] Although cinacalcet, a first-generation calcimimetic, efficiently lowers PTH, calcium, and phosphate levels, it has drawbacks, including gastrointestinal side effects (vomiting, nausea), food-dependent absorption, and drug-drug interactions (CYP2D6inhibition). Next-

generation calcimimetics have been created to get around these issues: To increase adherence, etelcalcetide, an intravenous calcimimetic, is given during haemodialysis.[6] Evocalcet is an oral medication with fewer drug interactions and improve gastrointestinal tolerability. Calcimimetics have thus made great progress in treating SHPT, increasing metabolic control and lowering consequences related to mineral bone abnormalities and chronic kidney disease.[1]

CALCIMIMETICS

Calcimimetics are substances that mimic or enhance the effects of extracellular Ca2+ on the CaR, which leads to decrease in PTH secretion and inhibition of the growth of parathyroid gland cells. Calcimimetics are a class of medications that function as allosteric activators of the parathyroid cells' calcium-sensing receptor (CaSR). They inhibit the release of parathyroid hormone (PTH), which helps regulate the balance of calcium and phosphate, by increasing the receptor's sensitivity to extracellular calcium.[3]

They are mostly used to treat secondary hyperparathyroidism (SHPT), a condition in which individuals with chronic kidney disease (CKD) have increased PTH levels, bone problems, and vascular calcification due to dysregulated calcium-phosphate metabolism.[8] Early attempts to treat SHPT by targeting the CaR resulted in the discovery of NPS R-568 (tecalcet), a calcimimetic drug that raised cytoplasmic Ca2+ concentration and suppressed PTH production in vitro when external Ca^{2+} was present.[3] NPS R-568 was created as the first calcimimetic drug; however, due to unfavourable pharmacokineticcharacteristics, includingavery poor bioavailability and being mostly metabolized by the highly polymorphic cytochrome P450 (CYP) enzyme, CYP2D6 (6), its clinical development was halted. Becausecalcimimetics attach to the parathyroid gland's calcium-sensing receptors, they decrease the generation of parathyroid hormone (PTH). In dialysis patients, secondary hyperparathyroidism (hyperPTH) is a common sign of bone and mineral disorders that can be managed with calcimimetics.[1]

1. TypeI Calcimimetics (Allosteric Modulators)

These agents interact with the transmembrane region of the calcium-sensing receptor (CaSR), increasing the receptor's sensitivity to extracellular calcium without directly activating it. By enhancing the receptor's response to calcium ions, they effectively suppress parathyroid hormone secretion.[6]

Common examples include

- **Cinacalcet**, the first-generation oral calcimimetic.
- **Evocalcet**, a newer oral agent designed to offer improved tolerability.
- **Etelcalcetide**, an intravenous peptide used primarily in dialysis patients.

2. Type II Calcimimetics (OrthostericAgonists)

These compounds bind directly to the extracellular calcium-binding site of CaSR, acting as calcium mimetics that activate the receptor independently. However, this class remains largely experimental with no approved drugs currently available for clinical use.[3]

PHARMACOLOGY AND MECHANISM OF ACTION

The calcium-sensing receptor (CaSR) is a G-protein–coupled receptor highly expressed on the parathyroid chief cells. It plays a central role in calcium homeostasis by detecting extracellular calcium concentrations and regulating parathyroid hormone (PTH) secretion.

Under normal physiological conditions, an increase in serum calcium activates the CaSR, which in turn suppresses the synthesis and release of PTH, thereby maintaining calcium balance. In patients with chronic kidney disease (CKD), hypocalcemia and phosphate retention lead to persistent stimulation of the parathyroid glands, causing secondary hyperparathyroidism (SHPT). This results in excessive PTH secretion, bone turnover abnormalities, and vascular calcification.

Evocalcet acts as a positive allosteric modulator of the CaSR. Unlike calcium ions, which bind to the orthosteric site, evocalcet binds to a distinct allosteric site within the transmembrane domain of the receptor.[6] This interaction increases receptor sensitivity to extracellular calcium, lowering the threshold for CaSR activation. Even at reduced calcium concentrations, evocalcet promotes CaSRsignaling via Gq/11-mediated activation of phospholipase C. The resulting generation of inositol triphosphate (IP_3) and diacylglycerol (DAG) triggers release of intracellular calcium stores, ultimately suppressing PTH synthesis and secretion.[3,6] By reducing circulating PTH levels, evocalcet helps restore calcium–phosphate balance, attenuates parathyroid hyperplasia, and decreases CKD-related bone and mineral abnormalities.[7]

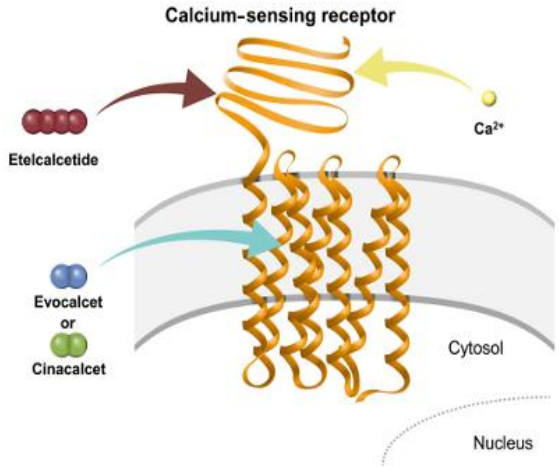
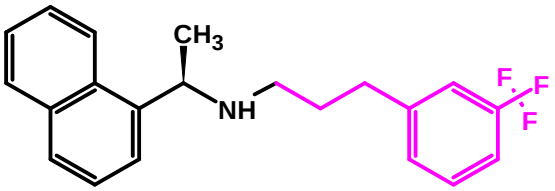


Figure 1: Mechanism of action of evocalcet.

CHEMISTRY AND SYNTHESIS

CINACALCET



IUPACNAME: *N-[(1R)-1-naphthalen-1-ylethyl]-3-[3-(trifluoromethyl) phenyl] propan-1-amine*

- **M.F:**$C_{22}H_{22}F_3N$
- **M.W:** 357.4 g/mol
- **SMILES:**C[C@H](C1=CC=CC2=CC=CC=C21)NCCCC3=CC(=CC=C3)C(F)(F)F

The US Food and Drug Administration authorized cinacalcet as the first calcimimetic medication in 2004 for the treatment of SHPT. Commercial availability began in the US in 2004, followed by Europe in 2005 and Japan in 2008.[6] Cinacalcet enhanced the percentage of patients who met the recommended goal ranges for serum PTH, calcium, and phosphate levels, suggesting that it also improved PTH and calcium and phosphate control.[7] VitaminD receptor activator (VDRA)-based treatments and the number of patients having parathyroidectomies have also significantly declined following the approval of cinacalcet. Cinacalcet lowers the risk of cardiovascular problems and inhibits the advancement of vascular calcification. An oral calcium analogue of NPS R-568, cinacalcet hydrochloride (cinacalcet) binds to the transmembrane domain of the CaR and lowers PTH, calcium, and phosphorus levels. It was demonstrated that CYP3A4, CYP2D6, and CYP1A2 metabolize it predominantly, removing the possibility of major adverse effects (AEs) from NPS R-568. Despite an improvement over NPS R-568, cinacalcet's bioavailability remained low.[6] Numerous clinical trials found that SHPT patients receiving cinacalcet had better results than those receiving a placebo or no cinacalcet medication. When it came to treating dialysis patients with SHPT, cinacalcet was the first calcimimetic medication to be approved globally. As demonstrated by the sharp decline in the rate of parathyroidectomies, which has remained low since cinacalcet's approval in Japan in 2008, patients with SHPT who previously uncontrollable nodular hyperplasia had were better managed; in 2008, there were 1059 cases, whereas in 2013, there were 276 cases.[7] Cinacalcet lowers serum PTH and calcium and phosphorus by inhibiting the expression of CaSR in the parathyroid glands. Cinacalcet does not raise serum calcium and phosphorus levels like analogues of activated vitamin D does. Comprehensive clinical studies have demonstrated that cinacalcet enhances clinical results and delays the beginning of cardiovascular events, which are the main reasons of which dialysis patients die.[3]

In two to six hours after oral treatment, cinacalcet reaches its maximal plasma concentration. A high-fat meal increases Cmax and the area under the curve (AUC) by 82% and 68%, respectively. With an initial half-life of roughly six hours, cinacalcet exhibits a decrease in biphasic concentration. Cinacalcet has a terminal half-life of roughly 30 to 40 hours. Within seven days, steady-state concentrations are reached. The range of doses from 30 to 180 mg per day does not alter the pharmacokinetic profile. The body contains large amounts of cinacalcet, with an apparent volume of distribution of about 1000 L. The binding of plasma proteins is between 93% and 97%. Renal excretion is the main method of elimination, with 15% of the dosage being eliminated in feces and 80% in urine.[6]

However, upper gastrointestinal adverse drug reactions (ADRs), such as nausea and vomiting, are common in individuals receiving cinacalcet. According to the EVO LVE research, patients who received cinacalcet experienced considerably higher rates of nausea and vomiting (29.1% and 25.6%, respectively) than those who received a placebo (15.5% and 13.7%, respectively). Such gastrointestinal intolerance restricts the cinacalcet dosage and may lead to noncompliance or cessation. Considering observations that cinacalcet inhibits stomach emptying in patients receiving haemodialysis, delayed gastricemptying appears to contribute to gastrointestinal side effects brought on by cinacalcet therapy.[3] Therefore, we postulated that abnormal GI motility could be a mechanism behind GI events and a reliable indicator of GI tract adverse effects. Additionally, cinacalcet inhibits cytochrome P450 (CYP) 2D6, which has led to discussions about possible medication interactions. Besides the adverse effects commonly linked with cinacalcet, its coadministration with drugs metabolized by CYP2D6—such as tramadol or codeine—may present additional challenges, as cinacalcet acts as a strong inhibitor of the CYP2D6 enzyme. The need for new calcimimetic drugs with a better profile or fewer side effects is unfulfilled because of the problems with cinacalcet.[4]

ETELCALCETIDE

- **CHEMICALNAME:***(2S)-2-amino-3-[(2R)-2-[(3S)-3-[(2-amino-2-oxoethyl) disulfonyl]-2-methylpropanamido] propyl] propanoic acid*
- **MOLECULAR FORMULA:** $C_{14}H_{24}N_4O_5S_2$
- **MOLECULAR WEIGHT**: 1048 g/mol
- **SMILES:**N[C@@H](CC(=O)N[C@@H](CC(C)C)C(=O)NCC(=O)N)C(=O)O

The creation of novel calcimimetics is necessary due to the possible disadvantages of cinacalcet stated. A newly created injectable calcimimetic called etelcalcetide functions as a direct agonist by binding to the extracellular domain of the CaR. Etelcalcetide (Parsabiv; Amgen, Thousand Oaks, CA, USA), formerly known as AMG416 or velcalcetide, is a novel second-generation calcimimetic used to treat SHPT in adult haemodialysis patients. It was approved in the US in February 2017, Japan in December 2016, and the EU in November

2016.[6,7] Etelcalcetide is a small peptide composed of eight amino acids with a molecular weight of 1,048 Da. Etelcalcetide's D-cysteine and the CaSR's extracellular domain's cysteine 482 form a covalent disulfide connection, which results in the CaSR's long-lasting allosteric activation.

The safety and effectiveness of etelcalcetide in HD patients with SHPT have been demonstrated in a number of clinical investigations. The first intravenous calcimimetic drug to be licensed for use in treating SHPT patients receiving haemodialysis was etelcalcetide in 2017. In comparison to placebo, etelcalcetide decreased serum iPTH levels and was linked to decreases in serum albumin-corrected calcium, phosphorus, and FGF-23, all of which are anticipated to enhance patient outcomes, according to Phase3research.[1,6] Etelcalcetide's noninferiority to cinacalcet was confirmed by a comparative study carried out in the US, Canada, Europe, Russia, and New Zealand. Over the course of 26 weeks, 57.7% of patients randomly assigned to cinacalcet and 68.2% of patients assigned to etelcalcetide saw a decrease in serum iPTH of at least 30%.[1] Etelcalcetide has emerged as a novel therapeutic option for patients who do not adhere to cinacalcet medication because it has been demonstrated to be at least as effective as cinacalcet. In CKD patients, etelcalcetide has a different pharmacokinetic profile than cinacalcet. The kidneys almost entirely eliminate etelcalcetide by glomerular filtration. Therefore, its plasma-elimination half-life, which has a short effective half-life of 3–5 days in patients with ESKD, increases dramatically with diminishing renal function. For patients receiving haemodialysis, a single intravenous dose can reduce PTH levels for up to 72 hours.[8] It can be administered intravenously three times a week at the conclusion of each haemodialysis session because of its prolonged half-life. Regular 4-hour haemodialysis sessions, three times a week, account for around 60% of the clearance of a single intravenous dose, while 31% is removed by nonspecific processes, Urine eliminates 3% of it, while faces eliminate 6%.[6]

For the treatment of SHPT in adult haemodialysis patients, etelcalcetide is a new second-generation calcimimetic that has been approved. Etelcalcetide is given intravenously three times a week at the end of the hemodialysate session, in contrast to cinacalcet, a first-generation calcimimetic, which is taken orally once daily.

In addition to enhancing medication adherence, etelcalcetide has demonstrated superior PTH lowering when compared to cinacalcet, with a similar and acceptable safety profile. Etelcalcetide has an additional role as a direct CaSR agonist, as it can activate the CaSR even in the absence of calcium, unlike cinacalcet.[7] In the Japanese Phase 3 research, which compared etelcalcetide with a placebo (no cinacalcet group), 1.3% and 3.8% of patients receiving etelcalcetide, respectively, experienced treatment-related adverse events (AEs). Unexpectedly, however, the prevalence of upper gastrointestinal illnesses associated with etelcalcetide use was nearly equal to that of cinacalcet in the comparative trial carried out overseas, leaving the problem of adverse reactions to calcimimetics unresolved.[6]

EVOCALCET

Since its approval in 2018, Evocalcet has only been marketed in Japan. Evocalcet (MT-4580/KHK7580) is a new oral calcimimetic that was created by testing its emetic impact in vivo and screening for its capacity to activate CaR in vitro.[3,6] In order to find new calcimimetic drugs without the negative effects of cinacalcet, we began investigating cinacalcet analogues as part of our early drug development efforts. The successful development of evocalcet resulted from attempts to enhance its CaSR agonistic activity, oral exposure, and CYP2D6 inhibition. It is the world's newest calcimimetic and was created in Japan to address the problems of cinacalcet's limited bioavailability, drug-drug interactions, and upper GI symptoms while maintaining its effectiveness in reducing PTH and improving SHPT. Since cinacalcet's GI side effects are difficult to endure, improving the safety profile is especially important for para dialysis patients.[7] Oral administration is recommended for para dialysis patients. Apart from suppressing PTH, this drug was chosen for more research due to its favourable profile, which was assessed by analysing its impact on rat stomach emptying and its interaction with CYPs in human liver microsomes. With cinacalcet serving as the comparative, the current phase 3 clinical trial used a double-dummy, double-blind design to examine the safety and effectiveness (noninferiority) of evocalcet.[3,6] Mitsubishi Tanabe Pharma Corporation in Osaka, Japan, synthesized evocalcet. Like cinacalcet, evocalcet is a chemical that contains naphthyl ethylamine skeletons. Numerous calcimimetics that have been documented in the literature bind to the transmembrane domain of CaR and are analogues of the phenylalkylamine chemotype, including NPS R-568.

Evocalcet was developed by creating cinacalcet analogues to lessen cinacalcet's off-target effects, which could be the cause of upper gastrointestinal illnesses. It has been discovered that adding a five-membered ring (pyrrolidine ring) to cinacalcet's structure reduces both its affinity for and inhibitory action on CYP2D6 by blocking the basic amine environment. Adjustments to the pyrrolidine ring's size and arrangement, as well as optimization of the carboxylic acid position, were made in order to increase bioavailability. The resultant substance, evocalcet, is composed of naphthyl ethylamine. Its basic nitrogen is thought to bind to the transmembrane domain of CaR and interact with Glu837, just like cinacalcet does.[3,6] The phenylacetic acid molecule produced by the aforementioned changes had significantly higher bioavailability, showing 84% bioavailability in rats as opposed to 1-2 percent for

cinacalcet. A mass balance study in humans revealed high bioavailability (62.7%), which was a notable improvement over cinacalcet (5–30%).[4] In order to prevent the deleterious effects of cinacalcet on the gastrointestinal tract, chemicals must be highly specifically exposed to the parathyroid gland. Reduced drug exposure in the central nervous system and gastrointestinal tract may also be significant.[6] Evocalcet provides more stable suppression of PTH levels with fewer peaks and troughs, reducing fluctuations that can affect bone metabolism. Lower rates of hypocalcaemia and better overall tolerability have been reported in comparison to other calcimimetics. Post-marketing surveillance and trials are underway to evaluate Evocalcet's efficacy and safety in broader patient populations and different ethnic groups.[5]

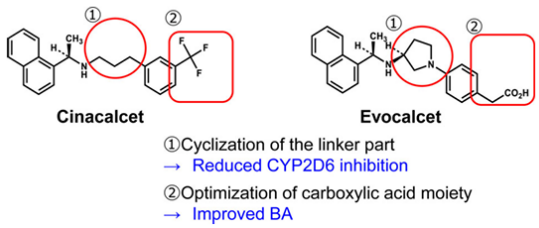
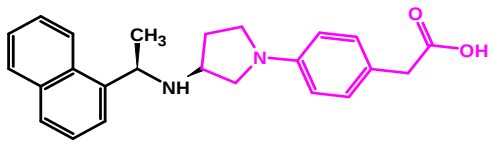


Figure 3: Cinacalcet Vs Ecocalcet.

STRUCTURE



Evocalcet.

- **IUPACNAME:***2-[4-[(3S)-3-[[(1R)-1-naphthalen-1-ylethyl] amino] pyrrolidin-1-yl] phenyl] acetic acid*
- **M.F:** $C_{24}H_{26}N_2O_2$
- **M.W**:374.5 g/mol

C[C@H](C1=CC=CC2=CC=CC=C21)N[C@H]3C CN(C3)C4=CC=C(C=C4)CC(=O)O

SYNTHESIS

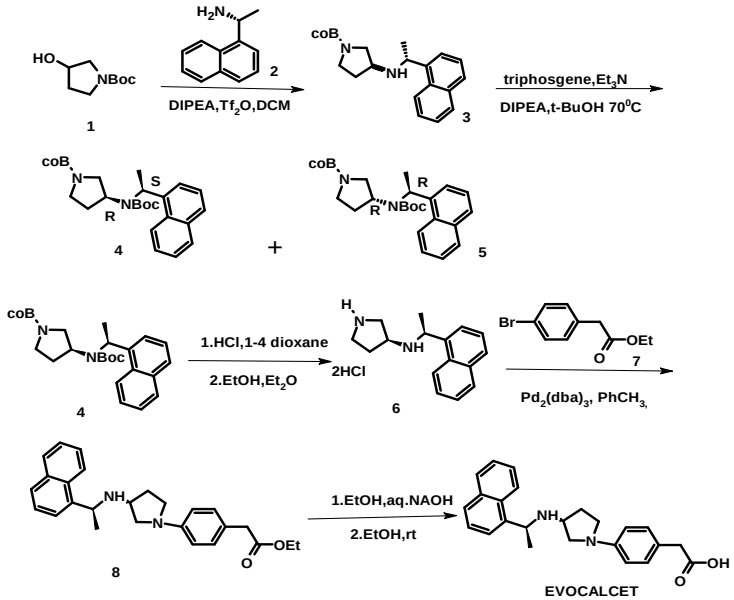
In order to reduce cinacalcet's off-target effects, which could be the cause of upper gastrointestinal diseases, evocalcet was developed using cinacalcet analogues. By blocking the basic amine environment, the addition of a five-membered ring (pyrrolidine ring) to the cinacalcet structure reduced its affinity for and inhibitory action on CYP2D6.[4] Adjustments to the pyrrolidine ring's size and shape, as well as optimization of the carboxylic acid position, were made in order to increase bioavailability. Evocalcet, the resultant chemical, is a naphthyethylamine. Like cinacalcet, its elemental nitrogen is assumed to attach to the transmembrane domain of the CaR and interact with Glu837 of the CaR.[3,6]

In a 2018 publication and patent, Kyowa Kirin and Mitsubishi Tanabe Pharma Corporation announced the discovery of evocalcet synthesis**.**

Evocalcet was developed by structural modification of cinacalcet. Incorporation of a pyrrolidine ring reduced CYP2D6 inhibition and improved oral bioavailability.

The synthetic route involves:

1. Activation of N-Boc pyrrolidine with triflic anhydride.
2. Coupling with (R)-(1-naphthyl)ethylamine.
3. Separation of diastereomers.
4. Triphosgene-mediated cyclization.
5. Global deprotection with HCl.
6. Buchwald–Hartwig amination.
7. Ester hydrolysis to yield evocalcet (overall yield ~73%).



Scheme 1: Synthesis of Evocalcet.

PHARMACODYNAMICS AND PHARMACOKINETICS

Evocalcet exhibits linear pharmacokinetics over the therapeutic dose range and achieves stable plasma concentrations with once-daily oral administration. Its pharmacokinetic properties allow effective control of parathyroid hormone (PTH) without the food-dependent absorption issues seen with cinacalcet.

Pharmacodynamically, evocalcet acts by enhancing the sensitivity of the calcium-sensing receptor (CaSR) to extracellular calcium, leading to sustained suppression of PTH secretion. This results in a dose-dependent reduction of serum PTH, calcium, and phosphate levels, with maintained efficacy during long-term therapy. Importantly, clinical studies demonstrate that evocalcet provides similar efficacy to cinacalcet but with improved tolerability, particularly reduced gastrointestinal adverse effects.

CLINICAL TRIALS AND COMPARATIVE ANALYSIS

In a Phase III Japanese multicenter trial involving 317 patients per treatment group, evocalcet demonstrated a non-inferior reduction in parathyroid hormone (PTH) levels compared to cinacalcet, while exhibiting a lower incidence of gastrointestinal adverse events (18.6% vs. 32.8%). Episodes of hypocalcemia were reported but were generally manageable with dose adjustments and calcium supplementation.

Compared with etelcalcetide, an intravenous calcimimetic administered thrice weekly, evocalcet provides the advantage of oral administration, offering greater convenience for patients requiring long-term therapy.

Table 1: Comparative clinical data of calcimimetics.

Parameter	Evocalcet	Cinacalcet	Etelcalcetide
Routeof administration	Oral	Once daily oral	IV thrice weekly
Phase III trial	317 patients	317 patients	Varies, typically HD patients
PTH secretion	Non-inferior to cinacalcet	Effective PTH reduction	Effective PTH reduction
Gastrointestinal Adverse effects	18.6%	32.8%	Lower than cinacalcet; IV route avoids GI events
Hypocalcemia Incidence	Manageable with dose adjustment & calcium	Manageable	Occurs; monitored closely

Table 2: Comparision ofcalcimimetics.

EVOCALCET	CINACALCET	ETELCALCETIDE
Second-generationcalcimimetic type-II small organic molecule	First-generationcalcimimetic type-II small organic molecule	Second-generationcalcimimetictype-II octapeptide
$C_{24}H_{26}N_2O_2$	$C_{22}H_{23}F_3N$	$C_{38}H_{73}N_{21}O_{10}S_2$
374.5 g/mol	357.4 g/mol	1048 g/mol
Allosteric modulator	Allosteric modulator	Allosteric modulator and direct agonist

SAFETY AND ADVERSE EVENTS

Calcimimetics are generally well-tolerated, but the most common adverse events include nausea, vomiting, diarrhoea, and hypocalcemia. Among available calcimimetics, evocalcet has been shown to cause fewer gastrointestinal adverse events compared to cinacalcet, which may improve patient adherence and quality of life.

Hypocalcemia is a known class effect of calcimimetics due to enhanced sensitivity of the calcium-sensing receptor (CaSR), but with evocalcet, most cases are mild to moderate and manageable through dose adjustment or calcium supplementation. Severe hypocalcemia is rare but requires prompt intervention.

Monitoring Recommendations

- Assess corrected serum calcium, phosphate, and PTH at baseline, 1–2 weeks after starting therapy or dose changes, and periodically thereafter.
- Temporarily hold or reduce the dose of evocalcet in patients who develop clinically significant hypocalcemia.
- Monitor for gastrointestinal symptoms, especially in patients switching from cinacalcet, as some may still experience mild nausea or vomiting.

ADVANTAGE OF EVOCALCET OVER CINACALCET

Cinacalcet and evocalcet have similar pharmacological profiles. Furthermore, evocalcet lowered serum PTH

levels more effectively than cinacalcet at a lower dosage. in rats, cinacalcet has a bioavailability of 1%–2%, but evocalcet has a bioavailability of over 80%.[3,6] it is hypothesized that this increased bioavailability helped lower the pharmacologically effective dose of evocalcet. Furthermore, because cinacalcet suppresses the CYP2D6 enzyme, drug-drug interactions also raised serious concerns. In terms of side effects, evocalcet outperformed cinacalcet in severalways.[4,6] Gastrointestinal symptoms, including nausea, vomiting, and stomach pains, are the primary side effects linked to cinacalcet. Additionally, cinacalcet has been shown to prevent stomach emptying in haemodialysis patients who experienced GI problems after taking it. However, even at a dose of 3 mg/kg, which is 100 times the amount needed to produce a noticeable PTH drop, evocalcet did not cause a delay in stomach emptying.[3] According to these results, cinacalcet had a greater effect on GI tract motility than evocalcet. Fewer animals experienced emesis when given evocalcet as opposed to cinacalcet. Based on these findings, it appeared that evocalcet had a greater margin of safety for emesis than cinacalcet.[1] A smaller dosage of evocalcet than cinacalcet may expose the GI tract less, which could explain the differences in how the two medications affect GI tracts. Even though the exact mechanism causing the nausea and vomiting associated with cinacalcet is still unclear, evocalcet's milder GI tract effects appear to have played a role in the decrease in GI events when compared to cinacalcet. The current study concluded by confirming the following in animals: The pharmacological profile of evocalcet indicates that it is an allosteric modulator on parathyroid cells, suppressing the serum levels of PTH; the GI tract was significantly less affected by evocalcet than by cinacalcet, which strongly suggests that evocalcet will have fewer GI side effects; and the pharmacokinetic profile was improved. Based on these results, evocalcet appears to be a safe and effective oral calcimimetic that can be used to treat CKD with SHPT.[1,3]

Marketed in China, Taiwan, South Korea, and Japan at the moment. To promote generic-by-brands and wider approvals, bioequivalence, pharmacokinetic, and Phase III trials are being conducted, particularly in China. Phase III trials conducted in Japan showed fewer gastrointestinal side effects and non-inferiority in PTH control when compared to Cinacalcet. Evocalcet exhibited strong CaSR agonistic effects and good PK profiles without any observable direct CYP inhibition.[3, 4] Evocalcet also outperformed cinacalcet in terms of a higher potential in vivo and fewer effects on GI tract symptoms. The next-generation allosteric CaSR agonist Evocalcet will offer SHPT a fresh therapeutic alternative.[6,7]

DRUG INTERACTIONS

Evocalcet exhibits minimal potential for clinically significant drug–drug interactions, which is highly advantageous for dialysis patients who are frequently on complex polypharmacy regimens.[4,6] Pharmacokinetically, Evocalcet is primarily metabolized by cytochrome P450 3A4 (CYP3A4), with minor contributions from CYP1A2 and CYP2D6. In vitro experiments have shown negligible inhibition or induction of major CYP isoenzymes, with only weak inhibition of CYP2D6 at supratherapeutic concentrations, suggesting that clinically relevant enzyme modulation is unlikely.

This favourable profile was confirmed in a Phase I clinical drug interaction (cocktail) study, where healthy volunteers were co-administered Evocalcet with probe substrates for CYP1A2 (theophylline), CYP2B6 (efavirenz), CYP2C8 (repaglinide), CYP2C9 (diclofenac), CYP2C19 (omeprazole), and CYP3A4 (midazolam). The pharmacokinetic parameters (AUC and Cmax) of all probe drugs remained within the bioequivalence range (0.8–1.25), indicating no clinically meaningful interactions, except for a slight (~25%) increase in theophylline exposure, which was not clinically significant.[6]

By contrast, cinacalcet, the first-generation calcimimetic, is a potent inhibitor of CYP2D6, which significantly alters the pharmacokinetics of several CYP2D6 substrates, including codeine, tramadol, and many antidepressants. Evocalcet's lack of strong CYP2D6 inhibition eliminates the need for dose adjustments when co-administered with these agents. Additionally, it can be safely combined with phosphate binders, vitamin D analogues, antihypertensives, and statins without requiring any modification in therapy. Therefore, Evocalcet offers a superior drug interaction profile compared to cinacalcet, reducing the risk of polypharmacy complications and improving the convenience of long-term therapy in secondary hyperparathyroidism patients undergoing dialysis.[4]

PHASE III TRIALS IN JAPAN

Multicentre study in **Japan, Duration 30 weeks**

In a phase 3 randomized, double-blind, double-dummy study, the safety and efficacy of the well-known cinacalcet and a new oral calcimimetic called evocalcet were compared. Evocalcet or cinacalcet (317 patients each) were randomly assigned to be administered for 30 weeks to Japanese haemodialysis patients with SHPT. The incidence of adverse events linked to the gastrointestinal tract was 18.6% and 32.8%, respectively (the difference between the groups was -14.2%[-20.9%, -7.5%], which is significant for superiority).[1]

Suppressing parathyroid hormone level was reached by 72.7% and 76.7% of the evocalcet and cinacalcet groups, respectively (between-group difference: -4.0% [95% Confidence interval -11.4%, 3.5%], indicating non-inferiority).

Therefore, these trials were Japanese multicenter Phase 3 studies that backed Evocalcet's 2018 approval for SHPT in dialysis patients in Japan.[6]

LIMITATIONS AND FUTURE DIRECTIONS

Current evidence for **evocalcet** is primarily derived from **Asian populations**, including patients from **Japan, South Korea, Taiwan, and China**. This geographic limitation may affect the generalizability of findings to other populations with different genetic, dietary, or healthcare factors.

Key gaps in knowledge include

- **Long-term cardiovascular outcomes** associated with sustained PTH reduction.
- **Impact on fracture risk** and bone mineral density in chronic SHPT patients.
- **Cost-effectiveness** compared with other calcimimetics and standard therapies in diverse healthcare settings.

To establish evocalcet as a **globally applicable therapy**, there is a need for:

- **Broader international clinical trials** including non-Asian populations.
- **Real-world observational studies** to assess long-term safety, adherence, and effectiveness.
- **Comparative health economic analyses** to guide cost-conscious treatment decisions.

CONCLUSION

A significant advancement in the management of secondary hyperparathyroidism in dialysis patients has been made with the advent of Evocalcet. By offering non-inferior parathyroid hormone (PTH) suppression compared to cinacalcet; while demonstrating improved gastrointestinal tolerability and reduced pill burden, it addresses key limitations of first-generation calcimimetics.[1,3] Its favourable pharmacological profile could potentially reduce healthcare burden associated with treatment discontinuation and side effects.[4] Continued post-marketing surveillance and real-world studies will be crucial to validate its long-term clinical and economic impact. Nevertheless, Evocalcet represents a valuable addition to the evolving landscape of calcimimetictherapy. Phase 3 clinical trials confirmed its efficacy, safety, and better patient adherence profile. Phase III trials in Japan have validated evocalcet's efficacy and safety, supporting its approval in multiple Asian markets including Japan, China, South Korea, and Taiwan.[1,6,7] Although further long-term data are needed to establish its cardiovascular outcomes and broader economic benefits, Evocalcet emerges as a promising alternative for optimized SHPT therapy, improving both biochemical control and patient quality of life. As international clinical trials progress, its approval in more countries is expected to expand therapeutic options for patients intolerant to cinacalcet. In the future, comparative studies on cardiovascular morbidity, fracture risk reduction, and cost-effectiveness will determine its broader clinical utility. Thus, Evocalcet not only addresses the unmet needs of existing calcimimetic therapy but also sets a benchmark for next-generation SHPT management in chronic kidney disease.[4,6] As clinical experience with evocalcet grows, it may also inform the development of future calcimimetics with tailored safety and efficacy profiles. Its role in combination therapy with other SHPT agents may further broaden its therapeutic applicability across diverse patient populations. However, current evidence is primarily limited to Asian populations, and long-term outcomes, including cardiovascular benefits, fracture risk reduction, and cost-effectiveness, remain to be fully established. Broader clinical trials and real-world studies are needed to confirm its role in global SHPT management.

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