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Anamorelin hydrochloride for the treatment of cancer-anorexia-cachexia (CACS) in nonsmall cell lung cancer

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Abstract

Introduction—Cancer anorexia-cachexia syndrome (CACS) is associated with increased morbidity and mortality. Anamorelin is a novel, orally active ghrelin receptor agonist in clinical development for the treatment of CACS in non-small cell lung cancer (NSCLC). The aim of this review is to summarize preclinical and clinical studies evaluating anamorelin as a potential promising treatment for CACS in NSCLC.

Area covered—Pharmacodynamics, pharmacokinetics and metabolism, clinical efficacy, safety, and tolerability of anamorelin for the treatment of CACS in NSCLC were reviewed. Anamorelin administration may lead to increases in food intake, body weight and lean body mass, and a stimulatory effect on GH secretion in NSCLC patients. Anamorelin is well tolerated with no dose-limiting toxicities identified to date.

Expert opinion—Targeting ghrelin receptors presents the advantage of potentially addressing multiple mechanisms of CACS simultaneously including appetite, muscle protein balance, adipose tissue metabolism, energy expenditure and inflammation. Clinical data suggest that anamorelin is well tolerated and it effectively increases appetite, body weight and lean mass in patients with advanced NSCLC. Long-term safety remains unknown at this time. The potential synergistic effects of anamorelin with nutritional support or exercise as well as its efficacy/safety in other tumor types are also unknown.

Keywords

Anamorelin; cancer-anorexia-cachexia syndrome; ghrelin; non-small cell lung cancer

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1. Introduction

Cancer anorexia-cachexia syndrome (CACS) has been recognized as an adverse consequence of cancer and its treatments and remains a challenging clinical syndrome. CACS is defined as a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (+/− fat loss) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment[1]. The weight loss criteria recommended is >5% over the previous six months or >2% in individuals already showing depletion according to current body-mass index (<20 kg/m^2) or skeletal muscle mass (sarcopenia)[1].

The incidence of CACS depends on the tumor type and ranges from 16% to over 50%[2, 3] being responsible for more than 30% of cancer-related deaths[3]. CACS is associated with poor quality of life (QoL), tolerance and response to anticancer therapy, and survival[4, 5]. Lung cancer is a leading cause of cancer death worldwide and non-small cell lung cancer (NSCLC) is the most common type of lung cancer. Despite recent advance in the treatment of NSCLC, the 5-year survival rate for patients with metastatic disease remains less than 20%[6, 7]. Approximately 60% of lung cancer patients show significant weight loss at the time of diagnosis, and more than 10% of patients die from CACS itself[3]. CACS and skeletal muscle wasting are commonly seen in NSCLC patients at baseline and are strongly associated with poor survival[8, 9]. Currently, the exact mechanisms underlying death due to cachexia has not been well-studied; however, these may include diaphragmatic muscle dysfunction[10] and poor nutritional status[11]. Diaphragmatic muscle weakness is associated with respiratory failure. Poor nutrition can lead to reduced immunity and increased susceptibility to infection.

The pathophysiology of CACS is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and hypercatabolism caused by systemic inflammation, tumor metabolism directly, and/or other tumor-mediated effects. Insulin resistance, prolonged high dose-corticosteroid therapy and hypogonadism may also contribute to catabolism[12].

The European Palliative Care Research Collaboration (EPCRC) treatment guidelines[13] recommend the treatment goal for cachexia should be the reversal of the loss of body weight and muscle mass through a multimodal approach. This includes detailed assessment and repeated monitoring, nutritional support, anti-inflammatory treatment, treatment of secondary gastrointestinal symptoms and other causes for decreased oral intake as well as evaluation of anti-neoplastic options to reduce the catabolic drive of the cancer. However, current treatment approaches for CACS are limited as there are no standard effective treatments for this condition.

1.1 Overview of current treatments

Treatment goals in CACS include improvements in appetite, lean body mass, resting energy expenditure, quality of life (QoL), performance status and inflammation[14, 15]. Adequate nutrition is essential in the treatment of these patients to ensure that malnutrition is not contributing to CACS even though patients do not appear to benefit from nutritional supplementation alone[16, 17]. Corticosteroids and progestins, such as megestrol acetate, are

the most widely used off-label treatment options and appear to stimulate appetite and increase fat mass, only partially alleviating CACS. Corticosteroids use is recommended for periods of only up to 2 weeks due to side effects, which include deterioration of muscle strength[3]. Recent evidence has also suggested a role for insulin resistance in CACS; insulin treatment has been found to potentially play a palliative role in CACS[18]. Drugs with a strong rationale that have not demonstrated consistent and convincing efficacy in clinical trials include melatonin[19], eicosapentaenoic acid[20], cannabinoids[21], bortezomib[22] and anti-cytokine therapies including thalidomide[23], and an anti-TNF-alpha monoclonal antibody (infliximab)[22]. The selective androgen receptor modulator (SARM) enobosarm showed good results in a phase 2 study[24] but failed to consistently improve the primary endpoints (lean body mass and stair climbing power) in phase 3 studies[25]. Several other targeted therapies are in clinical development. These include anti-IL-6 antibodies, cytokine antagonists, myostatin inhibitors and ghrelin/ghrelin mimetics.

1.2 Ghrelin and GHSR: Mechanisms of Action

Ghrelin is a 28 amino acid peptide that is the natural ligand for the growth hormone secretagogue receptor-1a[26, 27](GHS-R1a). Ghrelin plays an important role in several physiological processes including stimulation of appetite by stimulating the production of orexigenic mediators such as neuropeptide Y[28, 29]; by stimulating GH secretion and by regulating energy balance through GH-independent mechanisms[26, 30]. Ghrelin is produced primarily by the stomach and increases during periods of fasting or under negative energy balance. In contrast, ghrelin levels are low post-prandially and in obesity. Also, animal studies suggest that ghrelin may increase food reward via the mesolimbic dopamine system[31].

Ghrelin promotes adiposity through the activation of lipogenic pathways in the central nervous system (CNS)[32]. Ghrelin also activates white adipocytes, while inactivating brown adipocytes, resulting in decreased energy expenditure[33]. It also promoted lipogenesis and decreases lipolysis and lipid oxidation in white adipose tissue in an animal model of cisplatin-induced cachexia[34]. Ghrelin also stimulates gastric contraction and gastric emptying and its agonists are being developed for the treatment of gastroparesis and postoperative ileus[35, 36]. As nausea and constipation are common symptoms in cancer patients, these effects may be of further benefit in this setting.

Another important role of ghrelin in CACS treatment involves its anti-inflammatory actions[37]. Ghrelin exerted anti-inflammatory effects and attenuates endotoxin-induced anorexia in mice[38] and more recently in a murine model of cancer cachexia[39]. Ghrelin also inhibits the activation of nuclear factor-kB (NFkB), a transcription factor that stimulates the production of proinflammatory cytokines and increases muscle proteolysis[40]. A randomized clinical trial of the ghrelin mimetic MK-677 suggested that activation if GHSR-1a can also decrease energy expenditure as subjects receiving the active drug lost less weight upon caloric restriction than those receiving placebo[41].

The ghrelin receptor (growth hormone secretagogue, GHS-R1a) is a G protein-coupled receptor (GPCR) that is expressed in the central nervous system and in peripheral tissues. In the CNS, its expression is highest in several discrete hypothalamic nuclei, including the

anterior and lateral hypothalamic areas, and the ventromedial hypothalamus (VMH) and arcuate nuclei[42, 43]. GHS-R1a is co-expressed with both Neuropeptide Y (NPY) and growth hormone releasing hormone (GHRH), and ghrelin is thereby able to increase food intake and GH secretion[44, 45]. In peripheral tissues GHS-R1a is expressed in the anterior pituitary, pancreas[46], thyroid, spleen, myocardium and adrenal glands[47]. Notably, GHSR-1a receptor is not expressed in liver, skeletal muscle or adipose tissue[48]. Recent evidence suggest that ghrelin may have effects directly in adipocytes[49] and skeletal muscle[37, 39, 50], and an alternative, not yet discovered receptor has been proposed.

1.3 Clinical Trials of Ghrelin in Cancer Cachexia

In the setting of cachexia, data suggest that pharmacological doses of ghrelin may alleviate CACS and also are well-tolerated and safe in patients with advanced cancer. An acute, randomized, placebo-controlled, cross-over single dose clinical trial[51] performed in seven cancer patients showed a marked increase in energy intake (31±7%; P=.005) with a ghrelin infusion compared with saline. The meal appreciation score increased by 28±8% (P=.02) with ghrelin treatment and no side effects were observed. Another single-center randomized, double-blind, placebo-controlled, two-arm, double-crossover study[52] was carried out in 21 adult patients with advanced incurable cancer. Intravenous ghrelin infusion for 60 min at 2 or 8 mg/kg of body weight was well-tolerated and safe in these patients. More recently, a prospective, randomized phase 2 trial evaluated the effects of ghrelin during cisplatin-based chemotherapy in patients with advanced esophageal cancer[53]. Patients received either intravenous infusions of synthetic human ghrelin (3 μg/kg) or saline twice daily for 1 week with cisplatin administration. Food intake and appetite visual analog scale (VAS) scores were significantly higher in the ghrelin group than in the placebo group. Patients in the ghrelin group had fewer adverse events during chemotherapy related to anorexia and nausea than patients in the control group. The benefits from long-term provision of ghrelin for the treatment of CACS was also evaluated in a randomized, double-blind, phase 2 study[54]. Weight-losing cancer patients with solid gastrointestinal tumors were randomized to receive either high-dose ghrelin treatment (13 microg/kg daily; n=17) or low-dose ghrelin treatment (0.7 microg/kg daily; n=14) for 8 weeks as once-daily, subcutaneous injections. Appetite scores were increased significantly by high-dose ghrelin. High-dose ghrelin also reduced fat loss (P<.04) and increased serum GH (P<.05). There was a trend for high-dose ghrelin to improve energy balance (P<.07). Adverse effects were not observed by high-dose ghrelin in this study.

Taken together, data suggest that ghrelin may play an important role in stimulating appetite and food intake in CACS; however, the short half-life (<30 min), and the parenteral administration requirement of ghrelin has limited its clinical usefulness. Therefore, interest has switched to the development of orally-available ghrelin mimetics[55–57]. One of these mimetics, anamorelin (ONO-7643, formerly known as RC-1291), is a ghrelin receptor agonist currently in development for the treatment of non-small-cell lung cancer (NSCLC)-related cachexia.

2.1 Anamorelin: Chemistry

Anamorelin HCl (ANAM) is a potent and selective novel GHSR-1a agonist that is orally active and that mimics the N terminal active core of ghrelin. It has a longer half-life than ghrelin (7h vs. 0.5h)[58] and is currently undergoing evaluation as a potential treatment of CACS in Phase III clinical trials in NSCLC. The chemical name for anamorelin HCl is (3R)-1-(2-methylalanyl-D-tryptophyl)-3-(phenylmethyl)-3-piperidine-carboxylic acid 1,2,2-trimethylhydrazide hydrochloride (Figure 1)[58].

2.2 Pharmacodynamics

Anamorelin shows significant agonist activity on the ghrelin receptor with half-maximal effective concentration (EC_{50}) values of 0.74 nM[58], and no significant antagonist activity at concentrations of up to 1,000 nM. Anamorelin binds to the ghrelin receptor with a binding affinity constant (Ki) of 0.70 nM. In rat pituitary cells incubated with anamorelin, there was a dose-dependent stimulatory effect on GH release and the potency (EC_{50}) was 1.5 nM[58]. In vivo, when rats were treated with anamorelin 3, 10, or 30 mg/kg or vehicle orally, daily for 6 days, anamorelin significantly and dose-dependently increased food intake at all dose levels compared with controls. Administration of anamorelin at a single oral dose of 3, 10, or 30 mg/kg induced a dose-dependent increase in plasma GH levels. The maximum plasma GH concentration was reached at 0.5–2h postdose. Anamorelin stimulated a maximum increase in GH concentration ranging from 2.3-fold for the 3 mg/kg dose to 4.1-fold for the 30 mg/kg dose. Increases in GH and IGF-1 levels were also observed following anamorelin administration in pigs and dogs[58]. The implications of this GH increase from a safety perspective are discussed in section 2.5 Safety and Tolerability below.

2.3 Pharmacokinetics and metabolism

Pharmacokinetics of anamorelin was evaluated in phase I trials in healthy volunteers. Anamorelin administered in single doses of 10mg (n=6), 25mg (n=6), and 50mg (n=6) achieved plasma concentrations that peaked 0.5–2.0h post-dose[59]. Plasma half-life was approximately 7 hrs. Plasma was cleared of radio-labeled anamorelin by 18h post-dose with 99.8% of the drug recovered in feces (92%) and urine (8%). In order to assess the effects of food and CYP3A4 inhibition, subjects (n=13) received one 25-mg oral dose of anamorelin when fasted, fed (high-fat meal), and with ketoconazole. Plasma $AUC_{0\text{-}24h}$ values showed a 4-fold decrease with food and a 3-fold increase with ketoconazole.

2.4 Clinical Efficacy

2.4.1 Phase I studies—In a phase I randomized, double-blind, placebo-controlled single dose-rising study, 9 healthy male volunteers received 10, 25, and 50 mg oral doses of anamorelin. The 10-mg dose showed no effect. Pooled active doses (25 and 50 mg) indicated a rapid onset of response with significant appetite stimulating effect compared with placebo at 30 minutes; effect remained significant for 4 hours, the last time point assessed before eating. Spontaneous food intake increased 18.4% and was significantly greater than placebo. Dose-related increases in serum GH were recorded following placebo (5.38 ng/ml) and anamorelin 10 mg (23.68 ng/ml), 25mg (61.79 ng/ml), and 50 mg (88.15 ng/ml, p=.00009). Adverse events reported were: anamorelin–headache (n=4) and

stomachache (n=1); placebo–lightheadedness (n=1). All adverse events (AEs) were mild/moderate and resolved spontaneously. No dose-limiting toxicities were reported and no subjects discontinued anamorelin due to AEs[60].

In another randomized, double-blind, placebo-controlled, multiple-dose, dose-escalation phase I study in 29 healthy volunteers, anamorelin was well tolerated with no dose-limiting AEs. Anamorelin 50 or 75 mg induced significant dose-related weight gain after 6 days versus placebo, with the greatest increases seen with daily dosing. The mean increase in weight from baseline after 50 mg daily was 1.25±0.73 kg (p=.0022 versus placebo), and after 75 mg daily it was 1.16±0.65 kg (p=.0022 versus placebo)[55]. In the same study, single 25-mg, 50-mg, and 75-mg doses of anamorelin significantly increased circulating GH. The magnitude of this effect was attenuated with continued dosing. A robust increase in IGF-1 occurred after administration of the 50 mg and 75 mg doses of anamorelin[61]. One subject had moderate elevations in AST and ALT levels that normalized upon discontinuation of the drug. Other adverse events considered possibly related to study drug were: anamorelin-nausea, feeling hot, stomach discomfort, diarrhea (n=1 for each symptom), and headache (n=2).

2.4.2 Phase II studies in CACS—A phase II multicenter, double-blind, placebo-controlled, crossover study evaluated the acute effects of anamorelin in 16 patients with CACS. Patients were randomly assigned to anamorelin 50 mg/day or placebo for 3 days. A 3- to 7-day washout period followed and then treatments were switched. Anamorelin significantly increased body weight compared with placebo (0.77kg vs. −0.33kg, p value= 0.016). GH, IGF-1 and insulin growth factor binding protein-3 (IGFBP-3) significantly increased with anamorelin compared with placebo although levels remained within the normal range. Patient-reported symptoms as measured by the Anderson Symptom Assessment Scale (ASAS), significantly improved. AEs in four patients were possibly or probably related to anamorelin: hyperglycemia (n=2), nausea (n=1), and dizziness (n=1). Most AEs were mild[62].

More recently, two phase II multicenter, randomized, double-blind, placebo-controlled trials in 82 patients with incurable cancer were reported. The design of these trials was identical except that in one of them, patients enrolled in the 3-day cross-over trial described above were allowed after a wash-out period of at least 5 half-lives; data from these two trials were pooled a priori[63] Patients with different solid tumors were included in these studies. Pooled analyses showed that over 12 weeks, LBM measured by Dual-energy X-ray absorptiometry (DEXA) increased 1.89±0.53kg in the anamorelin group compared with a decrease −0.20±0.52kg in the placebo group (treatment difference of 2.09±0.58kg, p=0·0006). Increases in total body mass (TBM), appendicular LBM, handgrip strength and QOL were also noted. Scale weight was also higher and inflammatory cytokines lower in the anamorelin group, although the differences did not reach statistical significance. IGF-1 and IGFBP-3 also significantly increased at wks 4, 8, and 12, but remained within normal ranges. In this study, anamorelin was well tolerated, and AEs were similar between treatment arms[64]. Another international, randomized, placebo-controlled, multicenter, phase II trial evaluated the effect of anamorelin 50 mg (n=76) and 100 mg (n=73) vs. placebo (n=77) on body weight, HGS and quality of life as assessed by the MDASI score over 12

weeks. Patients in the ANA 100 mg group gained 0.14 kg, compared to mean losses of 0.3 kg and 1.32 kg for the 50 mg and placebo groups, respectively (mean treatment difference between 100 mg ANA and placebo was 1.47 kg; p = 0.0005). There were also improvements in HGS and MDASI scores in the ANA 100 mg dose group although these did not reach statistical significance. ANA was safe and well-tolerated in this study, and AEs of anorexia, nausea, and fatigue were reported in fewer ANA-treated than placebo-treated patients[65, 66].

2.4.3 Phase III studies—Two double-blind, Phase III trials (ROMANA 1, NCT01387269, n=484; ROMANA 2, NCT01387282, n=495) assessed the efficacy and safety of anamorelin 100mg in patients with incurable stage III/IV NSCLC and cachexia defined as ≥ 5% weight loss within prior 6 months or BMI <20 kg/m^2. Patients were randomized (2:1) to receive daily anamorelin or placebo for 12 weeks. Co-primary endpoints were change from baseline over 12 weeks in LBM (measured by DXA) and in hand-grip strength (HGS). Secondary endpoints included the anorexia-cachexia domain of the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) and the fatigue domain of the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F). In both studies, anamorelin increased LBM vs placebo (ROMANA 1: 1.10 kg vs −0.44 kg; ROMANA 2: 0.75 kg vs −0.96 kg; p<.0001 for both), but failed to show significant improvements in HGS[67]. Both studies also significantly improved FAACT anorexia/cachexia scores vs placebo, and increased body weight. In ROMANA 1, FACIT-F fatigue scores reached statistically significant differences at week 9 and week 12 only, but did not reach statistical significance over the entire 12 week treatment period. The most frequent drug-related AEs in both trials included hyperglycemia, nausea, and diabetes although their incidence were low (~2–5%). In ROMANA 3, over 500 patients who completed dosing in the ROMANA 1 or ROMANA 2 trials continued to receive their original treatment assigned for another 12 weeks to further evaluate efficacy and safety of anamorelin[68]. The independent data monitoring committee allowed the ROMANA 1–3 trials to continue as planned to completion.

2.5 Safety and Tolerability

In a phase I single dose study in healthy volunteers, AEs were mild and transient[60]. In a multiple-dose phase I study, all AEs were mild or moderate in intensity except for one event of severe headache reported that was not considered related to study drug. Effects on heart rate and blood pressure were modest and without clinical consequence. One subject had moderate elevations in AST and ALT levels that normalized upon discontinuation of the drug. Other adverse events considered possibly related to the study drug were: anamorelin-nausea, feeling hot, stomach discomfort, diarrhea (n=1 for each symptom), and headache (n=2). In the phase 3 studies, most frequent drug-related AEs were hyperglycemia (5.3%) and nausea (3.8%) for ROMANA 1, and hyperglycemia (4.2%) and diabetes (2.1%) for ROMANA 2. Both studies had few drug-related Grade ≥ 3 AEs (0.9%, 2.7%)[69]. The glucose-related AEs in Phase 3 trials are believed to be consistent with the mechanism of action of ghrelin, as ghrelin has been shown to regulate glucose metabolism through multiple pathways[70].

Concerns have been raised that administration of GHSR-1a agonists to cancer patients may potentially stimulate tumor growth. The effects of anamorelin and ghrelin on tumor growth were evaluated on A549 NSCLC xenographs in mice administered ghrelin (2mg/kg) or anamorelin (3–30mg/kg) for 28 days. Specifically, anamorelin increased GH concentrations by up to 2.5-fold, while repeated doses of ghrelin resulted in a maximum increase in GH concentrations of approximately 50-fold. For IGF-1, the mean concentrations were increased up to 122% and 109% in anamorelin and ghrelin groups respectively[71]. Neither ghrelin nor anamorelin treatment for 28 days affected tumor growth, as measured by tumor volumes, despite the significantly increased GH and IGF-1 levels. Also, clinical studies with 50 mg and 100 mg of anamorelin have shown no significant effect on long-term overall survival compared with placebo[65] although none of these studies have been adequately powered for this endpoint.

2.6 Long Term Effects

Long-term benefits of increasing LBM have not been well-established as effective treatments for cachexia are currently unavailable. Nevertheless there is an association between lean body mass loss and increased mortality in this setting[72]. Whether preventing or ameliorating cancer cachexia will lead to improved survival in clinical trials remain to be determined.

The effects of anamorelin on long-term prognosis and longevity have not been established. However, treatment with Rikkunshito, a ghrelin potentiator, was observed to prolong survival in an animal model of cachexia[73], and in a rodent model of cancer cachexia induced by Lewis Lung Carcinoma (LLC) tumor implantation, ghrelin administration prevented the development of cachexia (lean and fat mass loss) and this was associated with improved survival[39].

3 Conclusion

Given that CACS is a multifactorial syndrome and the complexity of this debilitating condition, therapeutic interventions for CACS are likely to require a multimodal treatment approach including a combination of proper nutrition, agents with orexigenic, anabolic, anti-catabolic and anti-inflammatory effects and also non-pharmacologic interventions (i.e. exercise). Ghrelin appears to play an important role in stimulating appetite and food intake, having anti-inflammatory actions and preventing losses in muscle mass and adiposity in the setting of cancer-related cachexia. Results to date indicate anamorelin is effective at stimulating appetite and increasing body weight and lean body mass with acceptable tolerability. However, there is a need to generate more clinical data to further explore its safety, efficacy and tolerability. Completion of the ROMANA 3 study and publication of the results of all phase III clinical trials are eagerly awaited.

4 Expert Opinion

CACS is an unmet clinical need that affects a large number of cancer patients. Although significant advances in this field have been made over the last decade increasing our understanding of how appetite, muscle and fat mass are regulated in this setting, these

efforts have fell short of delivering a drug to the market. Several molecular pathways are currently being targeted in clinical trials for this indication including some that are focused almost exclusively on muscle (i.e. myostatin, androgens), on inflammation (IL-1α) or through not well-characterized mechanisms (β-blockers, angiotensin-converting-enzyme inhibitors). Targeting ghrelin presents the advantage of potentially addressing multiple mechanisms simultaneously including appetite, muscle protein balance, adipose tissue metabolism, energy expenditure and inflammation. The orally available ghrelin receptor agonist anamorelin is the agent most advanced in its class for this indication. Clinical data published to this date suggest that anamorelin is well tolerated and it effectively increases appetite, body weight and lean mass in patients with advanced NSCLC. Long-term safety remains unknown at this time although more data will be available once ROMANA 3 is completed and presented. The functional impact of anamorelin also remains to be determined. Although it failed to show significant increases in HGS compared to placebo in phase III studies, this could represent lack of sensitivity of this test used to assess this outcome (handgrip), confounding due to other co-morbid conditions in a population with advanced cancer, or that longer exposure is required to see an effect in this domain. The potential synergistic effects of anamorelin with nutritional support or exercise as well as its efficacy/safety in other tumor types are also unknown. Future studies will be needed in order to address these questions.

5 Drug Summary box

Drug name (generic)	Anamorelin
Phase (for indication under discussion)	
Indication (specific to discussion)	NSCLC cachexia
Pharmacology description/mechanism of action	Anamorelin is a novel, potent and selective GHSR-1a agonist; it is orally active and effective at stimulating appetite and increasing body weight and lean body mass with acceptable tolerability.
Route of administration	Orally
Chemical structure	Figure 1
Pivotal trials:	Phase I, [55], [60], [61]. Phase II [62], [64], [65], and [66]. Phase III: [67] and [68].

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*=of important,

**=of considerable important

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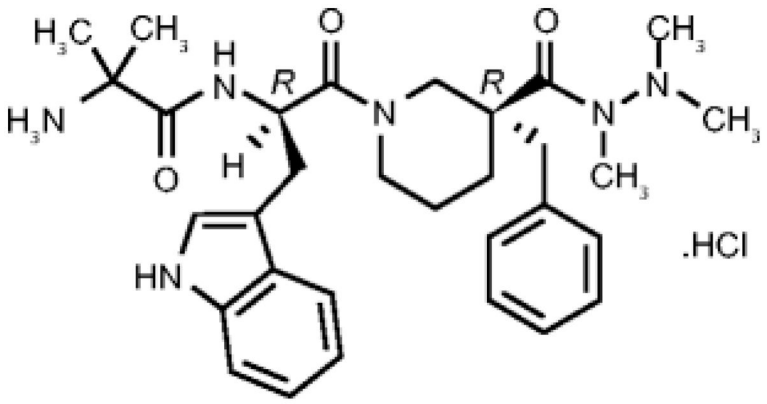

Figure 1.
Chemical structure of Anamorelin.
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