REVIEW

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Growth hormone secretagogues: history, mechanism of action, and clinical development

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Abstract

Growth hormone secretagogues (GHSs) are a generic term to describe compounds that increase growth hormone (GH) release. GHSs include agonists of the growth hormone secretagogue receptor (GHS-R), whose natural ligand is ghrelin, and agonists of the growth hormone-releasing hormone (GHRH) receptor, to which the GHRH binds as a native ligand. Several GHSs have been developed with a view to treating or diagnosing of GH deficiency, which causes growth retardation, gastrointestinal dysfunction, and altered body composition, in parallel with extensive research to identify GHRH, GHS-R, and ghrelin. This review will focus on the research history and the pharmacology of each GHS, which reached randomized clinical trials. Furthermore, we will highlight the publicly disclosed clinical trials regarding GHSs.

Keywords GHRPs; GHSs; Ghrelin; Morelins; Body composition; Growth hormone deficiency

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Introduction

The term growth hormone secretagogues (GHSs) embraces compounds that have been developed to increase growth hormone (GH) release. GHSs include agonists of the growth hormone secretagogue receptor (GHS-R), whose natural ligand is ghrelin, and agonists of the growth hormone-releasing hormone receptor (GHRH), to which the GHRH binds as a native ligand. Several GHSs have been developed with an aim to treat or diagnose GH deficiency, namely, growth retardation, gastrointestinal dysfunction, and altered body composition, in parallel with extensive research to identify GHRH, GHS-R, and ghrelin.

Ghrelin is a 28 amino acid-containing polypeptide that is mainly synthesized in the stomach. Its activity stimulates GH secretion and appetite, resulting in net body weight gain. From a historical angle, growth hormone-releasing peptides (GHRPs) were found prior to the discovery of ghrelin and the ghrelin receptor. Subsequently, GHSs, that is, ghrelin peptide mimetics, were developed. Only later, the GHS type 1a receptor (GHS-R1a) was discovered. Finally, ghrelin was successfully isolated as a natural ligand of GHS-R1a from stomach substrates in 1999. This background sparked the development of ghrelin receptor agonists, GHRPs, and GHSs; some of which reached testing in clinical trials. A vast array of indications of ghrelin receptor agonists has been evaluated including growth retardation, gastrointestinal dysfunction, and altered body composition; some of which have received approval by the Food and Drug Administration (FDA). This review will focus on the research history and the pharmacology of ghrelin receptor agonists. Publicly disclosed clinical trials regarding GHSs will be discussed in this regard.

History

In 1976, Bowers *et al.*[1] demonstrated that derivative forms of met-enkephaline selectively promoted GH secretion in rat pituitary cells, which indicated a therapeutic potential of a derivative of met-enkephaline as an alternative of GH replacement therapy, that used to be expensive and required a daily painful injection. Based on this concept, several novel derivatives of met-enkephaline were developed. Among them, GHRP6 and

GHRP2, reported in 1984 and 1992, respectively, have highly promoted GH secretion, compared with the natural GHRH.[2,3] Subsequently, GHS-R was cloned and shown to be the target of GHRPs in 1996.[4] Finally, ghrelin, an endogenous ligand of the GHRP receptor, was discovered in rat stomach by Kojima and Kangawa in 1999.[5] This progress of research regarding ghrelin and its related molecules is referred to a typical example of reverse pharmacology, namely, the discovery of GHSs was followed by the identification of the GHS-R and its endogenous ligand, ghrelin. Therefore, GHSs have been selected for clinical applications such as growth retardation, gastrointestinal dysfunction, and impaired body composition, in parallel with the exploratory research of endogenous substances.

Pharmacology

Because ghrelin has various physiological activities, ghrelin receptor agonists, mimicking the actions of ghrelin, represent pharmacological targets in several conditions. Here, we describe pharmacology of ghrelin receptor agonists in the following paragraphs, divided into three clinical indications, namely, growth retardation, gastrointestinal dysfunction, and impaired body composition. Chemical formula, synonyms, molecular weight, manufacturer (patent holder), route of administration, pharmacokinetics, and pharmacodynamics of GHSs are summarized in *Table* 1, and chemical structures of GHSs are depicted in *Figure* 1.

Table 1 Basic information of growth hormone secretagogues

Substance	Synonyms	Molecular formula	MW	First patent	Manufacturer	Route	Pharmacokinetics/pharmacodynamics
Sermorelin	GRF 1-29, Geref	$C_{149}H_{246}N_{44}O_{42}S$	3357.9	1990	EMD Serono	IV and SC	Humans. T_{max} 5–20 min. T1/2 11–12 min after SC administration.
Examorelin	EP-23905, 6003, Hexarelin	MF-$C_{47}H_{58}N_{12}O_6$	887.1	1994	Mediolanum Farmaceutici	PO and IN	Humans. After IV administration, plasma peak GH concentrations 30 min, half-life of GH 55 min.
Tabimorelin	NN-703	$C_{32}H_{40}N_4O_3$	528.7	1997	Novo Nordisk	PO	Inhibition of CYP3A4 activity.
Pralmorelin	Growth hormone-releasing peptide-2, KP-102, GPA-748	$C_{45}H_{55}N_9O_6$	818.0	2005	Kaken Pharmaceutical	PO and IV	Humans. IV administration, T1/2 0.42–0.69 h, mainly excreted in bile.
Ipamorelin	NNC 26-0161	$C_{38}H_{49}N_9O_5$	711.9	1998	Novo Nordisk and Helsinn Therapeutics	IV, SC, and IN	Humans. IV administration. T1/2 2 h, a clearance of 0.078 L/h/kg, a volume of distribution at steady-state of 0.22 L/kg. A single peak of GH release at 0.67 h.
Ulimorelin	TZP-101	$C_{30}H_{39}FN_4O_4$	538.7	2005	Lyric Pharmaceuticals and Tranzyme Pharma	IV	Small volume of distribution (99–180 mL/kg) following single IV administration in patients with gastroparesis, T1/2 10–20 h in healthy subjects.
Relamorelin	RM-131, BIM-28131, BIM-28163	$C_{43}H_{50}N_8O_5S$	791.0	2007	Ipsen and Rhythm Pharmaceuticals	SC	Humans. T_{max} 0.74 h, T1/2 ~4.5 h.
TZP-102	—	NA	NA	2009	Tranzyme Pharma	PO	N/A
Ibutamoren	MK-677, 163191	L-$C_{27}H_{36}N_4O_5S$	528.7	1995	Merck	PO	Beagles. After PO administration, plasma peak GH concentrations 120 min, half-life of GH 4–6 h.
Tesamorelin	TH-9507, Egrifta	$C_{223}H_{370}N_{72}O_{69}S$	5195.9	1996	Theratechnologies	SC	Bioavailability <4% after SC administration in healthy subjects. T_{max} 0.15 h. A volume of distribution 9.4 and 10.5 L/kg in healthy subjects and HIV-infected patients, respectively. T1/2 26 and 38 min, respectively.
Capromorelin	CP-424391, Entyce	$C_{28}H_{35}N_5O_4$	505.6	1997	Pfizer Aratana	PO, IV, and SC	Rats. After PO administration, T_{max} 1 h, T1/2 2.4 h,

(*Continues*)

Table 1 (continued)

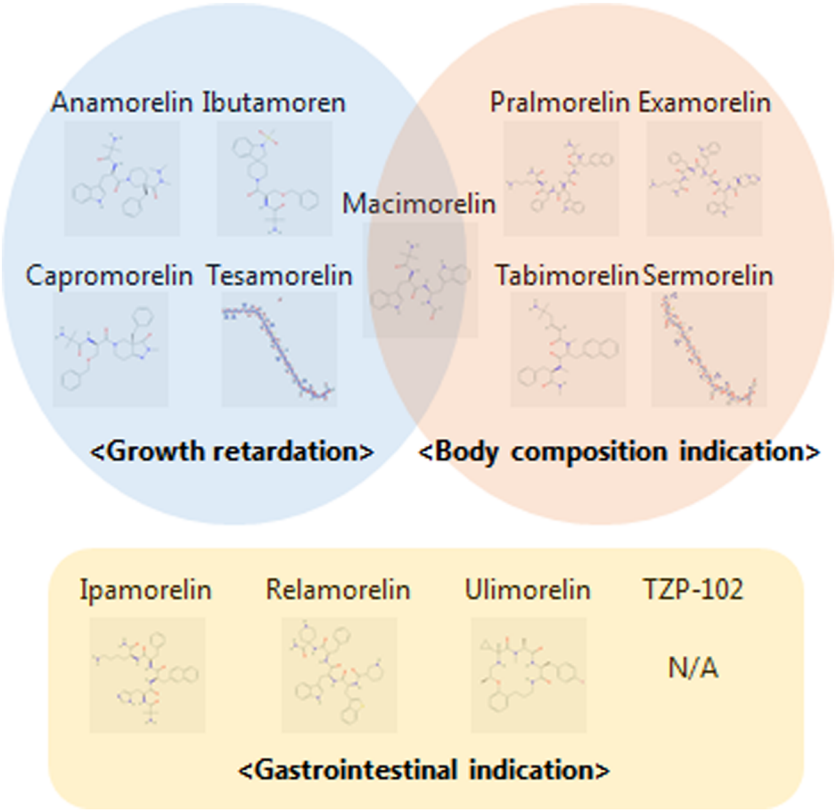
Substance	Synonyms	Molecular formula	MW	First patent	Manufacturer	Route	Pharmacokinetics/pharmacodynamics
							excretion: faeces (77–84%) and urine (7–15%).
Anamorelin	ONO-7643, RC-1291, ST-1291	$C_{31}H_{42}N_6O_3$	546.7	2003	Helsinn Therapeutics and Ono Pharmaceutical	PO	Humans. T_{max} 0.5–2.0 h, T1/2 7 h, excretion: faeces (92%) and urine (8%).
Macimorelin	AEZS-130, EP-1572, JMV1843, Macrilen	$C_{26}H_{30}N_6O_3$	474.6	2005	AEterna Zentaris	PO	Humans. PO administration. A single peak of GH release at 60–90 min.

Growth retardation: sermorelin, examorelin, tabimorelin, pralmorelin, and macimorelin

Sermorelin

Sermorelin is a 29 amino acids analogue of human GHRH with a fully functional activity of GHRH. In subcutaneous administration of 2 mg sermorelin, peak concentrations were reached in 5–20 min, and sermorelin was rapidly cleared from the circulation, with clearance values in adults ranging between 2.4 and 2.8 L/min. The half-life of sermorelin was short, 11–12 min after either intravenous or subcutaneous administration. Because sermorelin, intravenously or subcutaneously administered, specifically stimulates GH secretion from the pituitary gland without any significant change in prolactin, luteinizing hormone, follicle-stimulating hormone,

Figure 1 Chemical structures of GHSs. Chemical structures are provided by PubChem.[85] Blue, red, and yellow circles indicate a group of GHSs for the clinical indication of abnormal body composition, growth retardation, and gastrointestinal dysfunction, respectively.



insulin, cortisol, glucose, glucagon, or thyroid hormone levels,[6,7] sermorelin was approved for the treatment of growth retardation in children in 1997. However, sermorelin was discontinued in 2008 due to difficulties in the manufacturing process of the active ingredient used to produce commercially supplied sermorelin but not due to safety issues.

Examorelin

Examorelin, a hexapeptide, was derived from GHRP-6 by Mediolanum Farmaceutici in Spain.[8] Examorelin increased GH secretion *in vitro* and *in vivo* in a dose-dependent manner.[8,9] In healthy male adults, intravenous examorelin increased plasma GH values, which reached their peak value at approximately 30 min and decreased to baseline levels within 240 min with a half-life of ~55 min.[10] Examorelin was well tolerated, while examorelin experiences reversible diminished efficacy by 50–75% over the course of weeks to months.[11] Examorelin reached Phase II clinical testing for the treatment of GH deficiency, but the results have not been officially reported yet.[12] One study has discussed positive inotropic effects of examorelin for the treatment of heart failure.[13]

Tabimorelin

Tabimorelin, one of the first generation GHSs, was derived from ipamorelin by Novo Nordisk.[14] Tabimorelin increased GH release as well as production of insulin-like growth factor-1 (IGF-1) and IGF binding protein 3 (IGFBP-3) with subtle changes in adrenocorticotropic hormone, cortisol, and prolactin in healthy male subjects,[15,16] while only 11% of patients with GHD responding to tabimorelin with a peak GH concentration >5 μg/L.[17] Furthermore, tabimorelin was reported to inhibit CYP3A4, which may lead to unexpected side effects.[18] To overcome this drawback, Novo Nordisk has developed some compounds derived from tabimorelin including NNC-26-1167, although these have never been tested in clinical studies.

Pralmorelin

Pralmorelin, also known as GHRP2, is an orally active, short-acting, synthetic peptide that was originally developed by Polygen in Germany and Tulane University in the USA and then acquired by Kaken Pharmaceutical Company in Japan.[19] In rats, pralmorelin was associated with two-fold to three-fold increase in GH release compared with GHRP6 after intravenous administration. Plasma GH levels after a single pralmorelin administration were higher than 15 μg/L in healthy subjects, and lower than 15 μg/L values were observed in patients with severe GHD.[20]

Macimorelin

Macimorelin, an orally active small-molecule GHS, was developed through the modification of the tripeptide EP51389, which was synthesized by downsizing examorelin, by AEterna Zentaris in Canada. A previous study revealed that macimorelin, compared with examorelin and administered subcutaneously, significantly and selectively increased GH release in rats and healthy volunteers.[21] Subsequently, in a Phase I clinical testing, macimorelin increased serum GH levels in a dose-dependent manner, and GH levels remained high for approximately 120 min after oral or intraduodenal administration.[22]

Gastrointestinal indications: ipamorelin, ulimorelin, relamorelin, and TZP-102

Ghrelin has been shown to exert prokinetic effects on gastrointestinal motility via the vagus and pelvic nerve. Because the pharmacological potential of ghrelin is hampered by its short half-life, GHSs with enhanced pharmacokinetics were developed. Centrally penetrant GHSs stimulate defaecation and improve impaired bowel functions in animals and humans.[23]

Ipamorelin

Ipamorelin, a pentapeptide derived from GHRP-1, was originally developed by Novo Nordisk in Denmark.[24] Ipamorelin significantly and selectively increased plasma GH levels without any change in prolactin, follicle-stimulating hormone, luteinizing hormone, thyroid-stimulating hormone, adrenocorticotropic hormone, or cortisol levels in swines.[24] Ipamorelin induced GH release with a peak at 0.67 h after administration and a rapid decline in healthy subjects.[25] In a rat model of post-operative ileus (POI), repetitive intravenous ipamorelin administration was associated with a significant increase in faecal pellet output, food intake, and body weight gain.[26]

Ulimorelin

Ulimorelin, a small molecule GHS with low clearance (≈7 mL/h/kg), small volume of distribution (≈114 mL/kg), and a prolonged half-life of 10 to 20 h, was developed by the Canadian company Tranzyme Pharma.[27,28] Interestingly, ulimorelin improved decreased gastrointestinal motility without an increase in GH release in rats and humans.[29,30] In a clinical trial to investigate the safety and efficacy of ulimorelin in patients with diabetic gastroparesis, defaecation was significantly increased as a side effect, supporting a therapeutic potential for impaired lower gastrointestinal function such as POI and chronic constipation.[31] On the other hand, a recent study reported that ulimorelin could unexpectedly cause hypotension through the blockade of α_1-adrenoceptors.[32]

Relamorelin

Relamorelin, a synthetic pentapeptide, was developed by Rhythm Pharmaceuticals in the USA. Relamorelin binds to GHS-R with approximately three-fold higher affinity than ghrelin itself, and it increases plasma GH, prolactin, and

cortisol levels.[33] Moreover, relamorelin improved gastrointestinal motility with a 100-times greater potency compared with ghrelin in rat models of POI and morphine-induced ileus.[34] Relamorelin also promoted gastric emptying in patients with diabetic gastroparesis.[35,36] Based on these mechanisms and findings, relamorelin has drawn much attention as a therapeutic option for gastrointestinal dysfunction such as POI, diabetic gastroparesis, or chronic constipation.

TZP-102

TZP-102, a small molecule macrocyclic peptide, was developed as a second generation ghrelin agonist, following ulimorelin by Tranzyme Pharmaceutical.[37] TZP-102 is orally active and has a prolonged half-life.[37] TZP-102 reached Phase II clinical trials, although detailed information regarding TZP-102 has not been publicly disclosed.

Body composition indication: ibutamoren, tesamorelin, capromorelin, anamorelin, and macimorelin

Because both GH and IGF-1 increase muscle mass and muscle strength and decrease fat mass,[38–40] GHSs have been considered as drug candidates for the treatment of untoward alterations in body composition, such as HIV-associated lipodystrophy, sarcopenia, frailty, and cachexia. Ibutamoren, tesamorelin, capromorelin, anamorelin, and macimorelin have been tested in these clinical conditions.

Ibutamoren

Ibutamoren, a low molecular weight orally active GHS with a prolonged half-life, was developed by Merck in the USA.[41] Ibutamoren increases plasma levels of GH levels and IGF-1 without significant changes in cortisol values in beagle dogs and humans.[42–44] As a result, ibutamoren increased fat-free mass in obese subjects[43] and reversed diet-induced muscle wasting in healthy subjects under catabolic conditions.[45] On the other hand, ibutamoren was reported to be associated with an increased risk of heart failure in a randomized trial enrolling patients with hip fracture.[46]

Tesamorelin

Tesamorelin, a synthetic analogue of hGHRH with the addition of a trans-3-hexenoyl moiety to Tyr1 of the amino acid sequence, was developed by Theratechnologies, Inc. in Canada. Tesamorelin was resistant to dipeptidyl aminopeptidase-IV deactivation, resulting in a longer half-life compared with GHRH in animals and humans.[47,48] Because GHRH could be a better treatment option than GH replacement in HIV-infected patients with lipodystrophy,[49] tesamorelin has also progressed to clinical trial testing to examine the safety and efficacy in HIV-associated lipodystrophy.

Capromorelin

Capromorelin, an orally active GHS with a short half-life, was developed by Pfizer in the USA.[50] Because capromorelin increased GH and IGF-1 levels, resulting in body weight gain in rats and dogs,[51] the US FDA approved capromorelin as a therapeutic option for appetite improvement in anorexic dogs. Capromorelin is also considered as a drug candidate for the treatment of elderly subjects with sarcopenia and/or frailty.[52] However, it is unlikely that the agency will provide approval for this indication, because the aging process is *per se* not viewed as a pathological condition.

Anamorelin

Anamorelin, an orally active, small-molecule GHS with a prolonged half-life of 7 h, was developed by Helsinn Therapeutics.[53] Anamorelin increased plasma levels of GH, IGF-1, and IGFBP-3 as well as body weight in a dose-dependent manner without significant changes in the levels of other anterior pituitary hormones or glucose.[54,55] Anamorelin has progressed to Phase III clinical testing to examine the safety and efficacy in patients with non-small cell lung carcinoma (NSCLC)-induced cachexia[56,57]; however, the European Medicines Agency rejected the application for approval in fall 2017.

Results of major clinical trials and current status

Results of major clinical trials and current status of each GHS are summarized in *Tables* 2 and 3, respectively.

Growth retardation: sermorelin, examorelin, tabimorelin, pralmorelin, and macimorelin

Several clinical trials have been performed and completed to evaluate the safety and efficacy of GHSs for the diagnosis and/or treatment of GH deficiency, while most results have not been publicly disclosed, which indicate disappointing results, probably due to safety concerns or lack of efficacy over prolonged treatment, or due to unexpected side effects.

Sermorelin

Sermorelin was initially developed as a diagnostic tool for GH deciency.[58] Sermorelin rapidly and specifically increased GH release in healthy children but not in those with GH deficiency compared with existing provocative tests,[59] resulting in an approval for this indication by the FDA in 1990. Subsequently, 6 months treatment with sermorelin showed a significant increase in GH release and growth velocity in GH-deficient children,[60,61] and preliminary data suggested the efficacy of sermorelin treatment for 36 months.[59] Based on these findings, sermorelin was approved by the FDA for the

Table 2 Recent clinical trials of growth hormone secretagogues

Substance	Ref	Start date	CTI	P	Status	Number of patients	Route, dosage	Control regimen	Condition	F/U	Remarks
Ipamorelin	Bowers *et al.*[1]	2008, April	NCT00672074	2	C	114 in total	0.03 mg/kg	Placebo	Post-operative ileus	7 days	Ipamorelin was not effective for the treatment of post-operative ileus.
Ipamorelin	Bowers *et al.*[2]	2011, March	NCT01280344	2	C	320 in total	NA	Placebo	Gastrointestinal dysmotility	10 days	Ipamorelin did not improve any measurable gastrointestinal motility parameters.
Ulimorelin	Bowers[3]	2011, January	NCT01285570	3	C	332 in total	160, 480 μg/kg, IV	Placebo	Gastrointestinal dysmotility	7 days	Ulimorelin did not reduce the duration of post-operative ileus.
Ulimorelin	Bowers[3]	2011, February	NCT01296620	3	C	330 in total	160, 480 μg/kg, IV	Placebo	Gastrointestinal dysmotility	7 days	Ulimorelin did not reduce the duration of post-operative ileus.
Relamorelin	Howard *et al.*[4]	2011, July	NCT01394055	1	C	10/10	100 μg, SC	Placebo	Diabetic gastroparesis	2 days	RM-131 greatly accelerates the gastric emptying of solids in patients with type 2 diabetes and documented delayed gastric emptying.
Relamorelin	Kojima *et al.*[5]	2012, April	NCT01571297	2	C	68/68/68	10 or 20 μg, SC	Placebo	Diabetic gastroparesis	35 days	Relamorelin (20 μg daily) significantly accelerated gastric emptying and significantly reduced vomiting.
Relamorelin	Prakash and Goa[6]	2013, March	NCT01781104	2	C	25/23	100 μg, SC	Placebo	Chronic constipation	28 days	Relamorelin significantly reduced symptoms of constipation and accelerated colonic transit.
Relamorelin	Barron *et al.*[7]	2013, March	NCT01781104	2	C	12/6	100 μg, SC	Placebo	Chronic constipation	60 min	Relamorelin stimulated propagated colonic contractions without alteration of background irregular contractions.
Relamorelin	Carpino[8]	2015, July	NCT02466711	1	C	16	30 μg, SC	Placebo	Healthy	1 h	Relamorelin increased frequency of distal antral motility contractions without significant effects on amplitude of contractions.
TZP-102	Arvat *et al.*[9]	2009, April	NCT00889486	2	C	22/21/23/ 26	10, 20, and 40 mg, PO	Placebo		28 days	TZP-102 improved symptoms of gastroparesis, although symptom

(*Continues*)

Table 2 (continued)

Substance	Ref	Start date	CTI	P	Status	Number of patients	Route, dosage	Control regimen	Condition	F/U	Remarks
									Gastroparesis and diabetes mellitus		improvement was not consistent with change in gastric emptying.
TZP-102	Imbimbo *et al.*[10]	2011, September	NCT01452815	2	C	64 in total	10 mg, PO	Placebo	Gastroparesis and diabetes mellitus	4 weeks	TZP102 did not improve gastroparesis.
TZP-102	Imbimbo *et al.*[10]	2012, August	NCT01664637	2	T	67/67/67	10 and 20 mg, PO	Placebo	Gastroparesis and diabetes mellitus	12 weeks	TZP102 did not improve gastroparesis.
Ibutamoren	Rahim[11]	1998, July	NCT00474279	1/2	C	10/6	25 mg	Placebo	Elderly	4 weeks	Ibutamoren increased serum GH and IGF-I concentrations.
Ibutamoren	Broglio *et al.*[12]	2003, October	NCT00074529	2	C	416 in total	25 mg	Placebo	Alzheimer's disease	12 min	Ibutamoren did not inhibit the progression of Alzheimer disease.
Tesamorelin	Suckling[13]	2005, June	NCT00123253	3	C	275, 137	2 mg, SC	Placebo	HIV and lipodystrophy	26 weeks	Twenty-six weeks of tesamorelin decreased visceral fat and improved lipid profiles.
Tesamorelin	Hansen *et al.*[14]	2006, February	NCT00257712	2	C	14, 16	1 mg, SC	Placebo	Elderly, with and without mild cognitive impairment	30 weeks	Twenty weeks of tesamorelin administration increased GABA levels in several brain regions, increased NAAG levels in the frontal cortex, and decreased MI levels in the posterior cingulate.
Tesamorelin	Zdravkovic *et al.*[15]	2006, February	NCT00257712	2	C	14, 16	1 mg, SC	Placebo	Elderly, with and without mild cognitive impairment	30 weeks	Twenty weeks of tesamorelin administration had favourable effects on cognition in both adults with MCI and healthy older adults.
Tesamorelin	Zdravkovic *et al.*[16], Svensson *et al.*[17], and Zdravkovic *et al.*[18]	2007, August	NCT00608023, EudraCT2007–003233-16	3	C	TT 246/TP 135/PT 197	2 mg, SC	Placebo	HIV and lipodystrophy	52 weeks	Tesamorelin reduces visceral fat by approximately 18% and improves body image and lipid profile in HIV-infected patients with central fat accumulation. These changes are achieved without significant side effects or aggravation of glucose metabolism. Changes in lipid levels were associated with percentage change in VAT.
Tesamorelin	Furuta *et al.*[19]	2008, July	NCT00675506	2	C	29/29	2 mg, SC	Placebo	Obese subjects with reduced GH secretion	12 min	Tesamorelin selectively reduced VAT without significant effects on sc adipose tissue and reduced

(*Continues*)

Table 2 (continued)

Substance	Ref	Start date	CTI	P	Status	Number of patients	Route, dosage	Control regimen	Condition	F/U	Remarks
											triglycerides, C-reactive protein, and cIMT, without aggravating glucose.
Tesamorelin	Editorial[20]	2009, February	NCT00850564	1	C	13	2 mg, SC	Placebo	Healthy	4 weeks	Tesamorelin significantly increased GH and IGF-1, but not adiponectin.
Tesamorelin	Broglio *et al.*[21]	2009, February	NCT00795210	2	C	5/20	2 mg, SC	GH	HIV and lipodystrophy	2 weeks	Tesamorelin significantly increased overnight GH secretion but did not affect insulin sensitivity.
Tesamorelin	Piccoli *et al.*[22]	2010, December	NCT01263717	2	C	28/22	2 mg, SC	Placebo	HIV and lipodystrophy	6 min	Tesamorelin reduced visceral fat and liver fat.
Anamorelin	Pustovit *et al.*[23]	2010, December	JapicCTI-111415	2	C	31/42/42	50 and 100 mg, PO	Placebo	Cachexia associated with NSCLC	12 weeks	Anamorelin improved lean body mass, performance status, and QOL.
Anamorelin	Raun *et al.*[24]	2011, June	NCT00622193	2	C	73/76/77	50 and 100 mg, PO	Placebo	NSCLC	12 weeks	Anamorelin significantly increased body weight.
Anamorelin	Gobburu *et al.*[25]	2011, July	NCT01387269	3	C	323/161	100 mg, PO	Placebo	Cachexia associated with NSCLC	12 weeks	Anamorelin increased lean body mass but not handgrip strength.
Anamorelin	Gobburu *et al.*[25]	2011, July	NCT01387282	3	C	330/165	100 mg, PO	Placebo	Cachexia associated with NSCLC	12 weeks	Anamorelin increased lean body mass but not handgrip strength.
Anamorelin	Venkova *et al.*[26]	2011, July	NCT01395914	3	C	345/168	100 mg, PO	Placebo	Cachexia associated with NSCLC	24 weeks	Anamorelin significantly increased body weight.
Macimorelin	Wargin *et al.*[27]	2005, November	NCT00377377	1	C	36	Several doses, PO	Placebo	Healthy	4 h	Macimorelin rapidly and dose-dependently increased plasma drug concentrations and a potent GH release.
Macimorelin	Lasseter *et al.*[28]	2007, June	NCT00448747	3	C	50/48	0.5 mg/kg, PO	GHRH + arginine	AGHD and healthy	2.5 h	Macimorelin is effective in diagnosing AGHD with accuracy.

C, completed; R, recruiting; W, withdrawn; T, terminated.

Table 3 Licences and indications of growth hormone secretagogues

Substance	Status	Date	Clinical indications and descriptions
Sermorelin	Approved by FDA, then discontinued	2008, July	In September 1997, sermorelin was approved for the treatment of growth hormone deficiency in children with short statue by FDA. However, in 2008, EMD Serono. The drug will be discontinued because the active ingredient used to produce Gerer Diagnostic is no longer being manufactured.
Examorelin	Discontinued		
Tabimorelin	Discontinued?	N/A	It appears discontinued.
Pralmorelin (i.v.)	Approved in Japan	2004, October	Diagnosis of growth hormone deficiency in adults and children (>4 years old).
Ipamorelin	Discontinued		
Ulimorelin	Active	2017, March	To evaluate the effect of ulimorelin in patients with enteral feeding intolerance, participants are currently being recruited.
Relamorelin	Currently evaluated by FDA	2016, October	Treatment of diabetic gastroparesis.
TZP-102	Active	2013	FDA granted TZP-102 a fast track designation for the treatment of diabetic gastroparesis in 2009, but no recent development has been reported.
Ibutamoren	Discontinued		
Tesamorelin	Approved by FDA	2010, November	Reduction of excess abdominal fat in HIV-infected patients with lipodystrophy.
Capromorelin (oral)	Approved by FDA	2016, June	Appetite stimulation in dogs with decreased appetite.
Anamorelin	Requested for approval to EMA	2015, November	Cachexia associated with NSCLC.
Macimorelin	Requested for approval to FDA	2017, February	Diagnosis of growth hormone deficiency in adults.

treatment of idiopathic GH deficiency in children with growth failure in 1997.

Sermorelin was also tested in other clinical indications, namely, muscle wasting in elderly people with GH insufficiency, lipodystrophy in HIV-infected patients,[49] and impaired cognition in elderly subjects.[62] The results seemed promising, but further development has not been reported. In addition, sermorelin has been discontinued by EMD Serono in 2008, because of the supply issues of the active ingredient.

Examorelin

Examorelin reached Phase II clinical trials for the treatment of GH deficiency and that of congestive heart failure, but the results have not been disclosed. Finally, Mediolanum Farmaceutici discontinued producing examorelin for strategic reasons in 2005.[13]

Tabimorelin

Tabimorelin failed to show beneficial effects on GH release in adult patients with GHD in a Phase II trial.[17] Furthermore, tabimorelin was reported to inhibit CYP3A4, which may lead to unexpected side effects.[18] To overcome this drawback, Novo Nordisk has developed some compounds derived from tabimorelin, such as NNC-26-1167, although these have not been evaluated in clinical trials so far.

Pralmorelin

Plasma GH levels after single pralmorelin administration were higher than 15 μg/L in healthy subjects, while lower than 15 μg/L in patients with severe GHD,[20] which led to the approval of pralmorelin for the diagnosis of GHD in Japan in 2004.[63] Moreover, pralmorelin has been shown to stimulate growth velocity following 8 months of intermittent therapy in GHD children with intact hypothalamic–pituitary (H-P) axes.[64] Although pralmorelin reached Phase II clinical trials for the treatment of short statue, further development was discontinued. This was presumably because pralmorelin failed to increase plasma GH levels sufficiently in patients with GHD.[19]

Macimorelin

A Phase III clinical trial has shown that oral macimorelin was effective for the diagnosis of adult GHD with 82% sensitivity and 92% sensitivity at an optimal GH cut point of 2.7 ng/mL, which was comparable with GHRH and arginine test.[65] Another Phase III clinical trial has been completed in 2016, to compare its efficacy with the insulin tolerance test (ClinicalTrial.gov Identifier: NCT02558829), and AEterna Zentaris announced to pursue approvals of macimorelin for this indication by the FDA and the European Medicines Agency in March 2017. In addition, a Phase II clinical trial for the treatment of cancer cachexia is also currently ongoing (ClinicalTrial.gov Identifier: NCT01614990).

Gastrointestinal indication: ipamorelin, ulimorelin, relamorelin, and TZP-102

Ipamorelin

Ipamorelin was introduced to Phase II clinical trials for the treatment of POI, sponsored by Helsinn Therapeutics. However, in patients undergoing bowel resection, ipamorelin did

not shorten the time to first meal intake compared with placebo.[66] The following Phase II clinical trial did not show any significant difference in measurable colonic functions between ipamorelin and placebo.[67] Due to these disappointing results, its development was discontinued.

Ulimorelin

Based on the favourable effects of ulimorelin on gastrointestinal function in animal experiments and small clinical studies, ulimorelin has progressed to randomized clinical trials for the treatment of diabetic gastroparesis or POI. In patients with diabetic gastroparesis, ulimorelin improved gastrointestinal symptoms such as vomiting and appetite loss,[31] while there were no significant differences in improvement of gastrointestinal function between patients with POI taking ulimorelin and those taking placebo.[68] Because of this insufficient efficacy and the risk of unexpected hypotension,[32] its development for gastrointestinal indications has been discontinued.[69]

Relamorelin

A Phase I clinical trial showed that relamorelin, compared with placebo, greatly accelerated gastric emptying in female patients with diabetic gastroparesis.[35] Subsequently, a Phase II clinical trial demonstrated that relamorelin significantly reduced vomiting frequency and enhanced gastric emptying in patients with diabetic gastroparesis.[70] These results allowed the FDA to grant fast track designation for relamorelin for the treatment of diabetic gastroparesis in 2016.

The safety and efficacy of relamorelin on chronic constipation have also been evaluated. In a Phase II clinical trial, relamorelin significantly reduced the symptoms of constipation and accelerated colonic transit in female patients with chronic constipation.[71] Furthermore, the same study showed that relamorelin rapidly increased colonic contractions without any change in background irregular contractions.[72] These promising effects of relamorelin on gastrointestinal disorders might lead to a wider range of clinical applications in the near future.

TZP-102

A Phase IIa trial demonstrated that TZP-102 reduced abdominal symptoms without significant improvement in gastric emptying in patients with diabetic gastroparesis, compared with placebo.[73] Subsequently, Phase IIb trials failed to show significant difference in improvement of gastrointestinal motility between TZP-102 and placebo.[74] No developments regarding TZP-102 have been recently updated, because Ocera Therapeutics merged with Tranzyme Pharmaceutical, the manufacturer of TZP-102, in 2013.

Body composition indication: ibutamoren, tesamorelin, capromorelin, anamorelin, and macimorelin

Ibutamoren

In a randomized clinical trial, ibutamoren for 12 months was well tolerated and increased GH secretion and fat-free mass but not muscle strength in healthy elderly subjects.[75] However, further development was discontinued because ibutamoren was associated with the risk of heart failure in a randomized trial to examine the safety and efficacy in patients with hip fracture.[46]

Tesamorelin

Several randomized clinical trials have shown the beneficial effects of tesamorelin on impaired body composition in patients with HIV-associated lipodystrophy.[76–79] A meta-analysis including four clinical studies also revealed that tesamorelin decreased visceral fat and increased lean body mass in this population.[80] As a result, the FDA approved tesamorelin (Egrifta®) as the first-line treatment for the reduction of excessive abdominal fat in HIV-infected patients with lipodystrophy.

Capromorelin

A Phase II clinical trial investigated the effects of capromorelin on body composition and functional performance in healthy elderly subjects. At 12 months, capromorelin significantly increased lean body mass and stair climbing power compared with placebo. However, this study was terminated early, because the results at 12 months were deemed not indicate continuation of this study.[81] As aging the process is not considered a pathological condition by the FDA, capromorelin should offer outstanding results such as a survival benefit in this population or be applied for other clinical indications.[82] Capromorelin has so far been only approved by the FDA as a short-term therapeutic option for appetite improvement in anorexic dogs.

Anamorelin

Two double-blind, Phase III trials (ROMANA 1, NCT01387269, $n = 484$; ROMANA 2, NCT01387282, $n = 495$) assessed the efficacy and safety of anamorelin 100 mg in patients with incurable Stage III/IV NSCLC and cachexia defined as $\geq$5% weight loss within the previous 6 months or a body mass index <20 kg/m^2.[56] In both studies, anamorelin increased lean body mass compared with placebo (ROMANA 1: 1.10 kg for anamorelin, -0.44 kg for placebo; ROMANA 2: 0.75 kg for anamorelin, -0.96 kg for placebo; $P < 0.0001$ for both) but did not significantly improve handgrip strength.[56] Subsequently, an extension study, ROMANA3 (NCT01395914), enrolling 513 patients with NSCLC from ROMANA1 and ROMANA2, evaluated the efficacy and safety of anamorelin for an additional 12 weeks. As with prior studies, anamorelin

was associated with a favourable safety profile and increased body weight but not muscle strength.[83] Anamorelin has shown similar results in a clinical trial enrolling patients with NSCLC-induced cachexia in Japan [Clinical trial registration: JapicCTI-111415 (Japan Pharmaceutical Information Center Clinical Trials Information)].[84] Although several clinical studies have shown that anamorelin increased muscle mass, but not muscle strength, anamorelin has not been granted approval in 2017, despite the promising results in clinical studies, because increase in muscle mass without significant increase in muscle strength has not been considered acceptable.

Summary and outlook

Growth hormone secretagogues have been mainly selected for growth retardation, gastrointestinal dysfunction, and impaired body composition. However, in the field of growth retardation and gastrointestinal dysfunction, GHSs have failed to show favourable results in several clinical trials with an exception of pralmorelin, which was approved as a diagnostic tool for GH deficiency in adults and children in Japan. On the other hand, GHSs could be hailed as a promising treatment option for altered body composition. Tesamorelin has been approved by the FDA for the treatment of lipodystrophy in HIV-infected patients. Because exercise training and nutritional support have shown favourable effects on muscle wasting in impaired body composition such as sarcopenia and cachexia, combination therapy of GHSs such as anamorelin with them appear promising. A high medical unmet need in these pathological conditions should be further investigated in clinical trials.

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Conflict of interest

J. Ishida, M. Saitoh, and N. Ebner declare that they have no conflict of interest. S. von Haehling has been a paid consultant to Chugai Pharma and Helsinn Therapeutics.

The authors certify that they comply with the ethical guidelines for authorship and publishing of the *Journal of Cachexia, Sarcopenia and Muscle - Rapid Communications* (von Haehling S, Ebner N, Morley JE, Coats AJS, Anker SD. Ethical guidelines for authorship and publishing in the Journal of Cachexia, Sarcopenia and Muscle - Rapid Communications. JCSM Rapid Commun 2018; 1;e44:1–2.)

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