

Summary Report

Growth hormone-releasing peptide-2

Prepared for:

Food and Drug Administration

Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List

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Prepared by:

University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI)

University of Maryland School of Pharmacy

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Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GH	Growth hormone
GHRH	Growth hormone-releasing hormone
GHRP	Growth hormone-releasing peptide
GHRP2	Growth hormone-releasing peptide-2
GHRP6	Growth hormone-releasing peptide-6
IGF-1	Insulin-like growth factor-1
IRB	Institutional Review Board
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of growth hormone-releasing peptide-2 (GHRP2, also known as pralmorelin; UNII code: E6S6E1F19M), which was nominated for use as a bulk drug substance in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act.

The aim of this report was to describe how GHRP2 is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and healthcare practitioners were consulted to identify how GHRP2 has been used historically and currently.¹⁻³ Assessment of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.^{1,4,5} Rather, the aim was to summarize the available evidence on the use of GHRP2 and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATION

GHRP2 was nominated for inclusion on the 503B Bulks List by the Outsourcing Facilities Association (OFA). GHRP2 was nominated for use in combination with growth hormone-releasing peptide-6 (GHRP6) and sermorelin acetate (refer to Table 8).

GHRP2 was nominated for growth hormone deficiency (including adult onset), wasting syndrome, and anorexia nervosa via 0.5-5 mg oral tablets and capsules, aqueous solutions, aerosols for inhalation, and an injectable solution.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of GHRP2.⁶⁻¹⁰

Reasons provided for nomination to the 503B Bulks List included:

- GHRP2 is not commercially available as an FDA-approved product.
- Benefits include greater safety, less side effect, reactivation and stimulation of normal physiologic functions, multiple routes of administration, and broader spectrum of action.
- Compounded product may be the only product to effectively treat the indication for which it is intended.
- Patient need for dosage form or strength, including greater concentration, that is not available commercially.
- Patient sensitivities to dyes, fillers, preservatives, or other excipients in manufactured products.
- Manufacturer backorder.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of GHRP2 products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information, specifically, product trade name, active ingredient, strength, form, route of administration (ROA), and approval status, provided in a useable format. Based on these criteria, the

medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the EMA and the national registers of select EU countries (Ireland, UK, Belgium, and Latvia) were searched because some medicines were authorized for use in the EU and not available in a member country and vice versa.

Each medicine register was searched for GHRP2; name variations of GHRP2 were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing GHRP2. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe two concepts: GHRP2; and oral, inhalation or injectable administration, or diagnostic or therapeutic use (refer to Appendix 1 for full search strategies). Keywords for brand or proprietary products were not included in the search strategy because studies that utilized such products were excluded. Results were limited to human studies in English language. Searches were conducted on November 30, 2019. The reference lists of relevant systematic reviews and meta-analyses, retrieved in a separate search of Ovid MEDLINE on November 13, 2019, were reviewed to identify additional studies. In addition, the ECRI Guidelines Trust[®] repository was searched on November 30, 2019 for clinical practice guidelines that recommended the use of GHRP2 and provided sufficient dosing and administration instructions.

Results were exported to EndNote for Windows version X9.2 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which GHRP2 was used in the nominated dosage form, ROA, and/or combination product to diagnose, prevent or treat the nominated disease or condition, or other conditions not specified in the nomination, were included. Studies were excluded if they were: written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); designed to evaluate cost-effectiveness, mechanism of action, pre-clinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if GHRP2 was used as: a brand or proprietary product; an FDA-approved product in the nominated dosage form, ROA, or combination; or a dosage form, ROA, or combination that was not nominated. Studies in which GHRP2 was used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or historical use of the substance were noted and put in a separate group in

the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

Data extraction

The following information was recorded in a standard data extraction form: author names; article title; journal; year of publication; country; study type; historical use of GHRP2; setting; total number of patients; number of patients who received GHRP2; patient population; indication for use of GHRP2; dosage form and strength; dose; ROA; frequency and duration of therapy; use of GHRP2 in a combination product; use and formulation of GHRP2 in a compounded product; use of GHRP2 compared to FDA-approved drugs or other treatments; outcome measures; authors' conclusions. One reviewer extracted data from the included studies; a second reviewer checked the data extraction.

Interviews

Semi-structured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances GHRP2 was used in a clinical setting. The systematic literature review and indications from the nominations were reviewed to identify the following medical specialties that would potentially use GHRP2: endocrinology, naturopathy, pediatrics and neonatology, and primary care and internal medicine. Potential SMEs within the relevant medical specialties were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. In addition, the American Society of Health-System Pharmacists (ASHP) and select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were entered into NVivo 12 (QSR International) for qualitative data analysis. Several members of the research team independently coded the transcriptions of two representative interviews for themes. The team members discussed the codes that emerged from their independent analysis, as well as those codes that were determined a priori. The code book was developed out of the integration of these coding schemes.

Survey

A survey was distributed to the members of professional medical associations to determine the use of GHRP2 in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 2 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Year 1 were not contacted to distribute the project Year 2 surveys.

The survey was posted on the project website and the survey link was distributed to the associations that agreed to participate (refer to Appendix 3 for associations that participated and those that did not).

Participation was anonymous and voluntary. The estimated time for completion was 15 minutes with a target of 50 responses per survey.

The University of Maryland, Baltimore Institutional Review Board (IRB) and the FDA IRB reviewed the interview and survey methods and found both to be exempt. The Office of Management and Budget approved this project.

CURRENT AND HISTORIC USE

Results of background information

- GHRP2 is not available as an FDA-approved product in the nominated dosage form and ROA.
- GHRP2 is not available as an OTC product in the US.
- There is no current United States Pharmacopeia (USP) monograph for GHRP2.
- GHRP2 is not available in the nominated dosage form and ROA in any of the foreign registries searched.

Table 1. Currently approved products – US

No approved products in the US

Table 2. Currently approved products – select non-US countries and regions

No approved products in the selected non-US countries and region

Results of literature review

Study selection

Database searches yielded 392 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 267 titles and abstracts were screened. After screening, the full text of 36 articles was reviewed. Finally, 4 studies were included. Thirty-two studies were excluded for the following reasons: wrong study design (13 studies); GHRP2 used as brand or proprietary product (8); wrong indication (6); wrong dosage form or ROA (4); GHRP2 not used clinically (1).

Refer to Figure 1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Characteristics of included studies

The 4 included studies were published between 1995 and 2015. There were 3 experimental studies, and 1 descriptive study. The 4 studies were conducted in the following countries: Australia, Belgium, Japan, Russia, and US.

A total of 46 patients participated in the 4 included studies. The number of patients in each study ranged from 1 to 16.

Outcome measures differed among the included studies and included: acyl-ghrelin and desacyl-ghrelin levels in blood samples, height velocity, growth hormone levels, biochemical markers of catabolism and markers of anabolism.

Refer to Table 5 for summary of study country, design, patient population, intervention and comparator, and outcome measures.

Use of GHRP2

Thirty-one patients received GHRP2 as a treatment for short stature (idiopathic or due to growth hormone deficiency), administered intranasally in doses ranging from 10 mcg/kg/day to 45 mcg/kg/day, and intravenously at 1 mcg/kg. Duration of treatment ranged from once to 24 months.

One patient received GHRP2 as a treatment for anorexia nervosa, administered intranasally in doses ranging from 100 mcg/day to 700 mcg/day.

Fourteen patients received GHRP2 as an experimental treatment for wasting syndrome, administered intravenously in doses ranging from 1 mcg/kg to 1 mcg/kg/hour.

Refer to Tables 6 and 7 for summaries of dosage by indication.

GHRP2 was not used as a compounded product, nor was it used in a combination product.

In 4 studies, the authors' concluding statement recommended the use of GHRP2 for the treatment of short stature, anorexia nervosa, and wasting syndrome.

Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

In addition to the 4 included studies, several studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of GHRP2.

Growth hormone (GH), also known as somatotropin, is a protein that is produced by the somatotroph cells found in the anterior lobe of the pituitary gland. GH receptors are found throughout the body and are responsible for many metabolic functions including promoting growth in children, increasing lipolysis, stimulating protein synthesis, and antagonizing insulin.⁹ GH is regulated by 3 hypothalamic hormones: growth hormone releasing hormone (GHRH), somatostatin, and ghrelin.¹¹ GHRH and ghrelin stimulate GH release while somatostatin inhibits release.¹¹ GH has a pulsatile secretion with production occurring primarily at night and pulses following exercise, trauma, and sleep.⁹ GH production rises in childhood with the peak occurring at puberty and then declining with age. As GH declines with age, exogenous administration has many proposed benefits including increasing lean muscle mass, decreasing fat mass, increasing exercise tolerance, and increasing muscle strength.⁹ However, due to potential safety concerns associated with supratherapeutic GH levels resulting from the bypass of the normal, regulatory feedback, there has been an interest in the use of GH secretagogues.^{9,10}

GH secretagogues include GH-releasing peptides (GHRPs), like GHRP2 and GHRP6, and GHRH analogs, like sermorelin. GH secretagogues stimulate the endogenous secretion of GH, GHRPs increase the number of somatotrophs releasing GH and GHRH analogs increase the amount of GH secreted, which maintains levels within normal physiologic levels.^{9,12} The action of GHRPs is independent of GHRH so as a result, when a GHRH analog and a GHRP are used together they have a synergistic effect stimulating the release of GH.^{9,10}

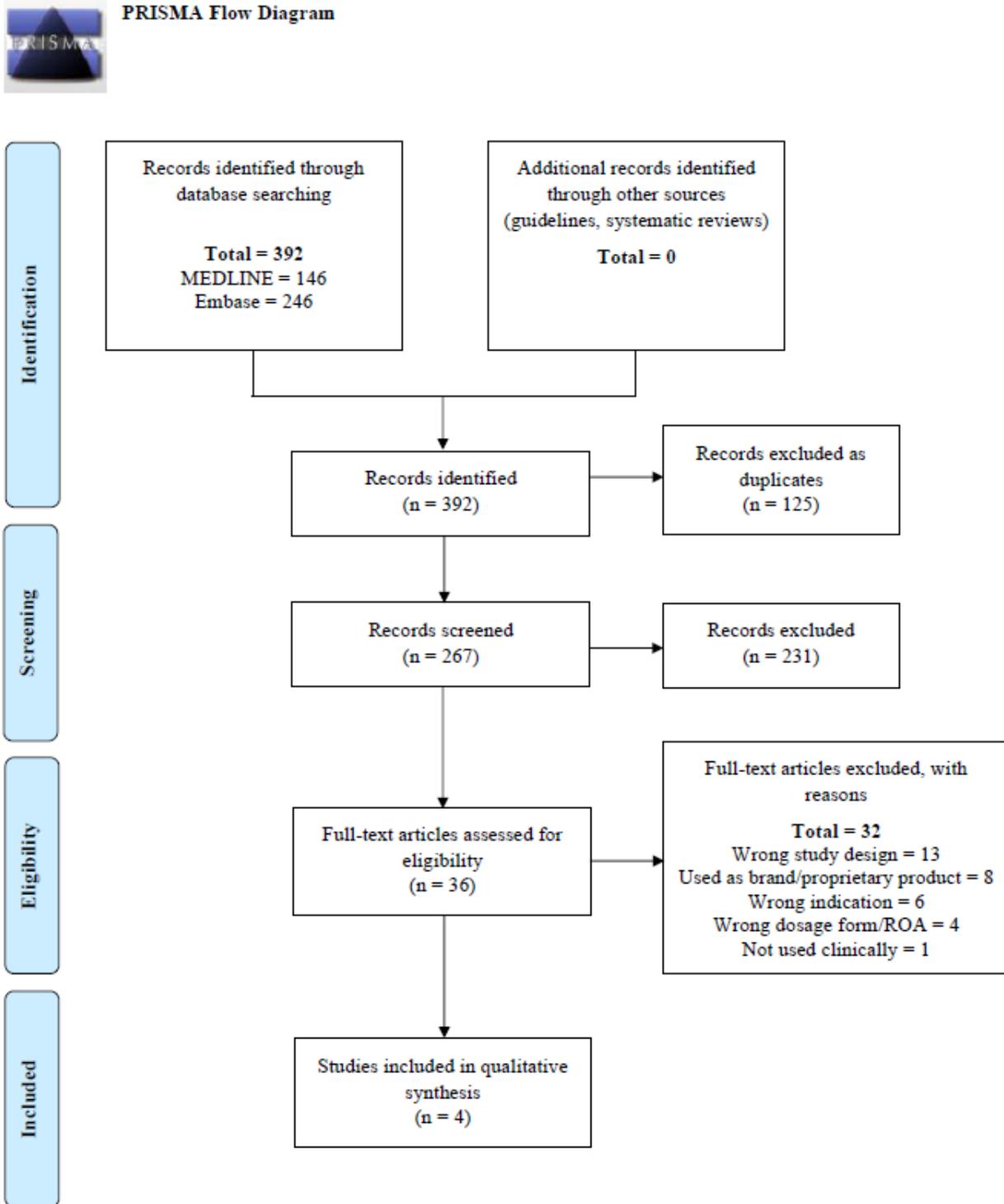
GHRPs were first synthesized in 1977 and GHRP6 was the first that was found to have significant in vivo activity; however, GHRP6 must be administered frequently and as an injection due to its poor oral bioavailability and short half-life.⁹ Additional research was conducted to identify subsequent molecules with a more favorable bioavailability and half-life resulting in the synthesis of numerous GH secretagogues.¹⁰ Based on the structure of GHRP6, new GH secretagogues were developed, including GHRP1 and GHRP2.¹³ GHRP2 is more potent than GHRP6 with a slightly longer half-life but due to a wide oral bioavailability it is still predominately administered as an injection.^{9,12}

Two studies evaluated the effect of GHRP2 on appetite. In the first study, 7 lean males were administered either GHRP2 at 1 mcg/kg/hr or saline for 270 minutes via a subcutaneous infusion and then their food intake was measured at an all-you-can-eat buffet style meal. The authors found that the participants administered GHRP2 ate significantly more than those who received saline. Additionally, GH levels rose significantly during the GHRP2 infusion as compared to saline.⁷ In the second study, the authors continued the previous study to include obese participants. Nineteen participants, 10 lean and 9 obese, were randomized to receive GHRP2 at 0.1 mcg/kg/hr, 1 mcg/kg/hr, or placebo via a subcutaneous infusion and then their food intake was measured. Similar to the first study, participants who received the GHRP2 infusion ate significantly more than those that received placebo, with obesity not having an impact on appetite. Both studies highlight the ability of GHRP2 to stimulate appetite and call for further studies to evaluate the potential use in malnutrition.¹⁴

Another study evaluated the use of GHRP2 in prepubertal GH deficient children. Six children were treated for 6 months with nightly subcutaneous injections of GHRP2. The dose increased every 2 months from 0.3 mcg/kg to 1 mcg/kg to 3 mcg/kg. The study found that GH levels increased in a dose-wise manner and growth velocity increased during the 6-month period as compared to pretreatment indicating that GHRP2 is able to stimulate GH secretion.¹⁵

Sigalos et al conducted a retrospective review of 105 hypogonadal men on testosterone therapy who were prescribed a combination of GHRP2 100 mcg / GHRP6 100 mcg / sermorelin 100 mcg subcutaneously 3 times a day in order to increase lean body mass and fat loss.¹⁰ Of these 105 men, 14 patients met the authors' inclusion criteria regarding adherence to the dosing regimen and baseline insulin-like growth factor 1 (IGF-1) levels less than 200 ng/mL were included in the study.¹⁰ IGF-1 is regulated by GH and due to the short half-life of GH, serves as a surrogate to assess GH levels.^{9,10} The authors evaluated the impact of the combination therapy on IGF-1 levels and found that it led to a significant increase in IGF-1 levels.¹⁰ The authors suggested that the combination therapy may be beneficial in wasting conditions where increases in fat-free mass are desirable.¹⁰

Figure 1. PRISMA flow diagram showing literature screening and selection.



Adapted from:

Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012. Available from: <http://www.prisma-statement.org/>.

Table 3. Types of studies

Types of Studies	Number of Studies
Descriptive ⁶	1
Experimental ¹⁶⁻¹⁸	3
Observational	0

Table 4. Number of studies by country

Country	Number of Studies
United States (US) ¹⁶	1
Multiple Countries <ul style="list-style-type: none"> • Australia, Belgium, US¹⁸ • Japan, US⁶ • Russia, US¹⁷ 	3
Total US ^a : 4 Total Non-US Countries ^a : 3	

^aStudies 6, 16, 18 counted in both US and non-US total

Table 5. Summary of included studies

Indication 1: Short stature					
Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Pihoker <i>et al.</i> , 1997, US ¹⁶	–	15 Pre-pubertal children at Tanner stage I (87%, 5-12 y)	<ul style="list-style-type: none"> GHRP2 (15) 	Height velocity	"All 15 children tolerated the intranasal GHRP-2 well, and readily accepted the intranasal spray...treatment with intranasal GHRP-2 produced a significant but modest increase in growth rate in this group of children."
Tuilpakov <i>et al.</i> , 1995, Russia, US ¹⁷	–	15 Children at Tanner stage 1 of puberty, 10 with short stature due to GHI (80%, 6.2-15.6 y), 5 with idiopathic short stature (80%, 6.9-13.6 y)	<ul style="list-style-type: none"> GHRP2 (15) GHRH (15) GHRP2 + GHRH (15) 	Peak serum level and AUC of growth hormone	Study demonstrated that GHRP2 can stimulate GH secretion in children with various forms of short stature.
Indication 2: Anorexia nervosa					
Haruta <i>et al.</i> , 2015, Japan, US ⁶	–	38-year-old woman with severely emaciated anorexia nervosa	<ul style="list-style-type: none"> GHRP2 (1) 	Acyl-ghrelin and desacyl-ghrelin levels in blood samples	"GHRP-2 increased appetite, body weight, and muscle strength, and improved fatigue, gastrointestinal functions, and hypoglycemia. The treatment was safe and tolerable without any obvious side effects."
Indication 3: Wasting syndrome					
Van den Berghe <i>et al.</i> , 1999, Belgium, US, Australia ¹⁸	–	14 Critically ill patients (71%, 44-81 y)	<ul style="list-style-type: none"> GHRP2 + TRH (14) Placebo (14) 	Biochemical markers of catabolism (urea production and urinary excretion of collagen cross-links) and anabolism (serum concentrations of osteocalcin, skeletal alkaline phosphatase, carboxyl-terminal extension peptide of type I procollagen, and leptin)	"The continuous infusion of GHRP-2 and TRH jointly for 5 days reactivated both axes, with preserved pulsatility and peripheral tissue responsiveness that were self-limited by apparently intact feedback inhibition loops that avoided overtreatment."

Abbreviations: "–", not mentioned; AUC, area under the curve; GH, growth hormone; GHI, growth hormone insufficiency; GHRH, growth hormone-releasing hormone; GHRP2, growth hormone-releasing peptide-2; TRH, thyrotropin-releasing hormone.

^aAs defined by authors.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Short stature (idiopathic and due to growth hormone deficiency) ^{16,17}	10-45 mcg/kg/day	–	Spray	Intranasal	6-24 months
	1 mcg/kg/day	–	–	Intravenous	Once
Anorexia nervosa ⁶	100-700 mcg/day	0.1%	Spray	Intranasal	10 months
Wasting syndrome ¹⁸	1 mcg/kg, 1 mcg/kg/h	50 mcg/mL	Solution	Intravenous	5 days

Abbreviations: “–”, not mentioned.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Short stature (idiopathic and due to growth hormone deficiency) ¹⁷	1 mcg/kg/day	–	–	Intravenous	Once
Anorexia nervosa ⁶	100-700 mcg/day	0.1%	Spray	Intranasal	10 months
Wasting syndrome ¹⁸	1 mcg/kg, 1 mcg/kg/h	50 mcg/mL	Solution	Intravenous	5 days

Abbreviations: “–”, not mentioned.

Table 8. Number of studies by combination

	Combination Formula	Number of Studies
Nominated	GHRP2 3 mg / GHRP6 3 mg / Sermorelin acetate 3 mg	0

Abbreviations: GHRP2, growth hormone-releasing peptide-2; GHRP6, growth hormone-releasing peptide-6.

Table 9. Compounded products – US

No compounded products from reported studies

Table 10. Compounded products – non-US countries

No compounded products from reported studies

Results of interviews

Two hundred eighty-five SMEs were contacted for interviews; 96 agreed to be interviewed, and 189 declined or failed to respond to the interview request. Four SMEs discussed GHRP2. The 4 SMEs were medical doctors. The SMEs specialized and/or were board-certified in endocrinology, naturopathy, and urology, working in academic medical center, private practice/clinic, and retired. The SMEs had been in practice for 8 to 43 years.

GH is commercially available as an FDA approved product, however, it has very narrow indications and is tightly regulated. When GH is administered exogenously as an injection, the natural secretion is inhibited. It was well known that morphine stimulates GH release and in the 1970's there was interest in the synthesis of opiate-like peptides and their potential ability to stimulate the release of GH. This led to the development of GHRP that was shown to “stimulate growth hormone without any analgesic effect and was not addictive.” In developing GHRP, researchers discovered that it worked on a secretagogue receptor separate from GHRH, which works on a GHRH receptor. In contrast to GH, when a GH secretagogue is administered it stimulates GH release and “the axis can respond to it” which “restores the growth hormone to what it should be and secreted, and that’s really important for normal growth.”

GH secretagogues may be used as single agents or in combination and are more often elective “patient demand-based medicine.” In many cases people seek these drugs as “lifestyle medications” to improve the appearance of their skin, hair, or body. One SME specializing in urology said that most of their patients come in with a hormone deficiency, which is usually testosterone. The patients are started on hormone replacement therapy and have positive results but still have a desire to improve their physical appearance, which may lead to prescribing GH secretagogues as a solution. In order to determine if a GH secretagogue would be appropriate, some SMEs may look at a patient’s IGF-1 level. The IGF-1 level is examined because growth hormones in the body have a half-life of 2-3 minutes, so “it’s very difficult to do a growth hormone assay.” IGF-1 has a half-life of 16-18 hours, according to one SME, so it provides “a good corollary for growth hormone effects.” If a patient starts with a low-normal to low IGF-1 level of less than 150 ng/mL, then they will likely benefit from a GH secretagogue.

One SME noted that GH and GH secretagogues address a more limited set of symptoms to make a patient feel better, look better, or mitigate muscle loss. There have been some studies that have shown that when GH secretagogues are used together they have a synergistic effect. For example, GHRP2 or GHRP6 in combination with sermorelin leads to a “stronger growth hormone response, or growth hormone secretory response.” These synergies are the result of “receptor interactions in the growth pathway that will accentuate the response.” They amplify the response on the receptor and interact at different receptors, stimulating different methods of releasing growth hormone. By combining hormones which have different molecular effects on the pathways, a synergistic effect can be achieved. A “trending” combination right now is CJC-1295 (a GH secretagogue) and ipamorelin. Ipamorelin inhibits somastatin, a “downstream inhibitor of the growth hormone pathway,” which results in “stepping on the gas” and

“releasing the brake” to create a synergistic effect. An SME specializing in urology used the combination of GHRP2 / GHRP6 / sermorelin for weight loss and to improve sperm count in morbidly obese men, and for men with hypogonadal symptoms with “low or borderline IGF-1 levels.”

There is “limited literature” about the specific dose and/or combination of GHRPs that should be used. Additionally, most of the literature focused on “what’s the impact going to be on the growth hormone pathway” and not the downstream effects (i.e., simulate muscle growth, fat loss, other measurable effects). As a result, patients are typically started on a low dose that can then be titrated up as needed. The typical dosing for injectable GHRP is 100-500 mcg/day with up to 1,000 mcg/day with sermorelin. The dosage is gradually increased if they patients do not develop side effects. For both adult and pediatric patients, GH secretagogues, especially GHRP2 and GHRP6, require multiple doses per day for “optimal effects.” The circadian rhythm of the growth hormone pathway involves numerous “peaks and troughs throughout the day.” This makes in-office dosing impossible. The secretagogues are administered subcutaneously, which “can be done very easily at home.”

There is a “dose response effect” beyond which the body will no longer respond to more medication, which impacts dosing. There are typically few side effects and “it’s very hard to overshoot.” The feedback mechanism of the secretagogues is intact, making it difficult to “overtreat patients” and offering a safety device to clinicians. To measure outcomes, SMEs may track IGF-1 levels but, “it takes a while for IGF-1 to actually go up.” One SME noted that some clinicians will monitor progress by the physical changes a patient experiences since they “prescribe these types of medications for patients who want a desired physical outcome” instead of IGF-1 levels.

Three of the 4 SMEs had used the GH secretagogues GHRP2 and GHRP6. While there is limited literature to base clinical decisions on, “there are informed decisions that are being made” regarding their use. One SME stated that the lack of literature does not mean these drugs should not be used, stating that the drugs are “much safer than growth hormones, because they’re stimulating the natural pathway,” instead of shutting it down and overriding the natural pathway, like with GH. The SME continued that “anecdotally over the years...they [GH secretagogues] seem to work as advertised, and they seem to be quite safe, but we don’t have the peer review literature to prove that, just yet.” The SME who did not use growth hormones cited a risk of promoting malignancy, a lack of evidence-based research, and expense.

Summary of survey results

Zero people responded to the survey distributed via professional medical associations and available on the project website.

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which GHRP2 / GHRP6 / sermorelin acetate prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded GHRP2 / GHRP6 / sermorelin acetate

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded GHRP2 / GHRP6 / sermorelin acetate

No respondents to survey distributed via professional medical associations

CONCLUSION

GHRP2 was nominated for inclusion on the 503B Bulks List as oral tablets and capsules, aqueous solutions, aerosols for inhalation, and injectable solutions to treat growth hormone deficiency (including adult onset), wasting syndrome, and anorexia nervosa. GHRP2 is not available in the nominated dosage forms and ROA in any of the national medical registries searched.

In the 4 studies included from the literature review, GHRP2 was used for treatment of short stature, and to stimulate appetite and increase body weight and muscle mass in patients with anorexia nervosa or critical illness. Additional studies were identified in which the effect of GHRP2 was evaluated in lean and obese people, children with GH deficiency, and hypogonadal men on testosterone therapy. From the interviews, three SMEs had used GHRP2 and 1 had used the GHRP2 / GHRP6 / sermorelin combination. The SME who used the GHRP2 / GHRP6 / sermorelin combination prescribed it for patients who were obese and/or had hypogonadal symptoms and wanted to lose weight and improve their sperm count. Several SMEs stated that there was limited outcomes-based human research on the clinical use of GH and GH secretagogues, making it difficult to know the ideal combination and dose of medication to use, and the effects of long-term use. One SME stated that this did not mean that GH secretagogues should not be used because they appear quite safe, only that more research on their use is needed.

Zero people responded to the survey distributed via professional medical associations and available on the project website.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process and other non-indexed citations and daily 1946 to November 27, 2019
- Date last searched: November 30, 2019
- Limits: Humans (search hedge); English language
- Number of results: 146
- Notes: Tested with terms for route of administration and therapeutic or diagnostic use as second concept. Difference in number of results was not significant. Therefore, did not add second concept. Investigational drug numbers included due to small number of results.

1	growth hormone releasing peptide 2.tw.	61
2	GHRP 2.tw.	191
3	GHRP2.tw.	6
4	pralmorelin.tw.	12
5	kp 102.tw.	24
6	kp102.tw.	9
7	gpa 748.tw.	2
8	gpa748.tw.	0
9	or/1-8	222
10	exp animals/ not humans/	4646734
11	9 not 10	149
12	limit 11 to english language	146

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: November 30, 2019
- Limits: Humans (search hedge); English language
- Number of results: 246
- Notes: Investigational drug numbers included due to small number of results.

1	pralmorelin'/de	324
2	growth hormone releasing peptide 2':ti,ab,tn	66
3	ghrp 2':ti,ab,tn	216
4	ghrp2':ti,ab,tn	10
5	pralmorelin':ti,ab,tn	16
6	kp 102':ti,ab,tn	45
7	kp102':ti,ab,tn	9
8	gpa 748':ti,ab,tn	4
9	gpa748':ti,ab,tn	0
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	380
11	drug administration route'/de	7709
12	oral drug administration'/de	403470
13	parenteral drug administration'/de	2047
14	intramuscular drug administration'/de	71382
15	intravascular drug administration'/exp	415798
16	respiratory drug administration'/exp	3237
17	subcutaneous drug administration'/de	100716
18	drug administration':lnk	1687505
19	inhal*':ti,ab	156847
20	oral*':ti,ab	920843
21	inject*':ti,ab	1062540
22	infusion*':ti,ab	346804

23	(parenteral* NEAR/2 (administ* OR therap* OR treat* OR deliver*)):ti,ab	17821
24	subcutaneous*:ti,ab	240061
25	intravenous*:ti,ab	473351
26	intra venous*:ti,ab	1408
27	intravascular*:ti,ab	65819
28	intra vascular*:ti,ab	665
29	intramuscular*:ti,ab	72345
30	intra muscular*:ti,ab	1253
31	drug therapy'/de	681571
32	add on therapy'/de	18175
33	drug indication'/de	62158
34	hormonal therapy'/de	44134
35	hormone substitution'/de	36368
36	drug therapy':lnk	3774607
37	therap*:ti,ab	3963810
38	treat*:ti,ab	7640923
39	diagnostic test'/de	78366
40	endocrine function test'/exp	102457
41	test*:ti,ab	4361319
42	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41	15471494
43	#10 AND #42	332
44	[animals]/lim NOT [humans]/lim	5957252
45	#43 NOT #44	251
46	#43 NOT #44 AND [english]/lim	246

Appendix 2. Survey instrument for professional medical associations

Welcome. We want to understand your clinical use of compounded growth hormone-releasing peptide-2 (GHRP2/Pralmorelin) in combination with GHRP6 and sermorelin acetate. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email:
compounding@rx.umaryland.edu.

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Thank you,

Dr. Ashlee Mattingly
Principal Investigator
The University of Maryland School of Pharmacy

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

2. Do you prescribe or administer GHRP2 / GHRP6 / sermorelin acetate as a combination product to your patients?

- Yes
- No

3. I prescribe or administer GHRP2 / GHRP6 / sermorelin acetate as a combination product for the following conditions or diseases: (check all that apply)

- Anorexia nervosa
- Growth hormone deficiency
- Wasting syndrome
- Other (please describe) _____

4. I use compounded GHRP2 / GHRP6 / sermorelin acetate as a combination product because: (check all that apply)

- Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
- Patient allergies prevent me from using commercially available products. (please explain) _____
- Patient conditions prevent me from using commercially available products. (please explain) _____
- There are no commercially available products containing GHRP2 / GHRP6 / sermorelin acetate.
- Other (please explain) _____

5. Do you stock non-patient-specific compounded GHRP2 / GHRP6 / sermorelin acetate as a combination product at your practice?
- Yes
 - No
 - I'm not sure
6. I obtain compounded GHRP2 / GHRP6 / sermorelin acetate as a combination product from the following: (check all that apply)
- Compound myself at my practice
 - Have the product compounded by an in-house pharmacy
 - Purchase, or have a patient purchase, from a compounding pharmacy
 - Purchase, or have a patient purchase, from an outsourcing facility
 - Other (please explain) _____
7. What is your practice setting? (check all that apply)
- Physician office/private practice
 - Outpatient clinic
 - Hospital/health system
 - Academic medical center
 - Emergency room
 - Operating room
 - Other (please describe) _____
8. What degree do you hold? (check all that apply)
- Doctor of Medicine (MD)
 - Doctor of Osteopathic Medicine (DO)
 - Doctor of Medicine in Dentistry (DMD/DDS)
 - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
 - Naturopathic Doctor (ND)
 - Nurse Practitioner (NP)
 - Physician Assistant (PA)
 - Other (please describe) _____

Appendix 3. Survey distribution to professional associations

Specialty	Association^a	Agreed/Declined, Reason for Declining
Allergy/Immunology	American Academy of Allergy, Asthma, and Immunology (AAAAI)	Declined – survey not approved
Anesthesia	American Society of Regional Anesthesia and Pain Medicine (ASRA)	Declined – failed to respond
	Society for Ambulatory Anesthesia (SAMBA)	Declined – failed to respond
	Society for Neuroscience in Anesthesiology and Critical Care	Declined – failed to respond
Critical Care	Critical Care Societies Collaborative	Declined – failed to respond
Dentistry & Oral Medicine	Academy of General Dentistry (AGD)	Declined – provided interview referrals
	American Dental Association (ADA)	Declined – failed to respond
Dermatology	American Academy of Dermatology (AAD)	Agreed
	American Osteopathic College of Dermatology (AOCD)	Declined – not interested
Endocrinology	The Endocrine Society (ENDO)	Agreed
	Pediatric Endocrine Society	Agreed
Gastroenterology	American Gastroenterological Association (AGA)	Declined – failed to respond
	Obesity Medicine Association (OMA)	Declined – did not have anyone to contribute to research
Hematology	American Society of Hematology (ASH)	Declined – does not distribute surveys
Infectious Disease	American Academy of HIV Medicine (AAHIVM)	Declined – failed to respond
Medicine	American Medical Association (AMA)	Declined – failed to respond

Naturopathy	American Association of Naturopathic Physicians (AANP)	Agreed
	The Oncology Association of Naturopathic Physicians (OncANP)	Agreed
Nephrology	American College of Clinical Pharmacists: Nephrology Practice Network	Agreed
	American Society of Nephrology	Declined – provided interview referrals
Nutrition	American Society for Parenteral and Enteral Nutrition (ASPEN)	Declined – provided interview referrals
Obstetrics and Gynecology	American Gynecological and Obstetrical Society (AGOS)	Declined – failed to respond
	Nurse Practitioners in Women’s Health	Agreed
Ophthalmology	American Academy of Ophthalmology (AAO)	Agreed
Otolaryngology	American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)	Declined – survey not approved
Pain Management	American Academy of Pain Medicine (AAPM)	Declined – survey not approved
	American Academy of Physical Medicine and Rehabilitation	Declined – failed to respond
Pediatrics and Neonatology	American Academy of Pediatrics (AAP)	Agreed
Primary Care	American College of Physicians (ACP)	Declined – failed to respond
Psychiatry	American Academy of Clinical Psychiatrists	Declined – failed to respond
	American Association for Geriatric Psychiatry	Declined – failed to respond
Rheumatology	American College of Rheumatology (ACR)	Agreed

Surgery	Ambulatory Surgery Center Association (ASCA)	Agreed
	American Academy of Orthopaedic Surgeons (AAOS)	Declined – no interest in participation from members
	American Association of Hip and Knee Surgeons (AAHKS)	Declined – only send surveys from members
	American College of Surgeons (ACS)	Agreed
	American Society for Metabolic and Bariatric Surgery (AMBS)	Declined – only send surveys from members
	The Association of Bone and Joint Surgeons	Declined – failed to respond
	Physician Assistants in Orthopaedic Surgery	Declined – failed to respond
	Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)	Declined – failed to respond
	Society of Gynecologic Surgeons (SGS)	Declined – policy limits number of surveys per year and do not have a method to identify if any of the SGS members are using ipamorelin
Toxicology	American Academy of Environmental Medicine (AAEM)	Declined – failed to respond
Urology	Sexual Medicine Society of North America (SMSNA)	Agreed

^aAssociations that declined in Year 1 were not contacted in Year 2.