



(51) International Patent Classification:

A61K 39/395 (2006.01) A61P 3/10 (2006.01)
C07K 16/28 (2006.01)

(21) International Application Number:

PCT/US2018/013918

(22) International Filing Date:

16 January 2018 (16.01.2018)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/447,332 17 January 2017 (17.01.2017) US

(71) Applicant: AMGEN INC. [US/US]; One Amgen Center Drive, Thousand Oaks, California 91320 (US).

(72) Inventors: CHENG, Yuan; 5329 Via Jacinto, Newbury Park, California 91320 (US). NETIROJJANAKUL, Chawita; 4631 Kester Ave., Apt. 103, Sherman Oaks, California 91403 (US). HOLDER, Jerry Ryan; 1102 Waltham Road, Simi Valley, California 93065 (US). WU, Bin; 3090 Hollycrest Avenue, Thousand Oaks, California 91362 (US). FALSEY, James R.; 13209 Peach Hill Road, Moorpark, California 93021 (US). HERBERICH, Bradley J.; 1746 Hays Drive, Newbury Park, California 91320 (US). SHAM, Kelvin; 3111 La Casa Court, Thousand Oaks, California 91362 (US). MIRANDA, Leslie P.; 3586 Mapleknoll Place, Thousand Oaks, California 91362 (US). LU, Shu-Chen; 2356 Rutland Place, Thousand Oaks, California 91362 (US). VENIANT-ELLISON, Murielle M.; 645 Camino Manzanitas, Thousand Oaks, California 91360 (US). STANISLAUS, Shanaka; 4196 Minnecota Drive, Thousand Oaks, California 91360 (US). YIE, Junming; 4 Sugarwood Way, Warren, New Jersey 07059 (US). XU, Jing; 67 Bishops Forest Drive, Waltham, Massachusetts 02452 (US).

(74) Agent: DERMOTT, Jonathan M. et al.; One Amgen Center Drive, Patent Operations, MS-35-1-B, Thousand Oaks, California 91320 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP,

KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

Published:

— with international search report (Art. 21(3))
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
— with sequence listing part of description (Rule 5.2(a))

(54) Title: METHOD OF TREATING OR AMELIORATING METABOLIC DISORDERS USING GLP-1 RECEPTOR AGONISTS CONJUGATED TO ANTAGONISTS FOR GASTRIC INHIBITORY PEPTIDE RECEPTOR (GIPR)

(57) Abstract: Methods of treating metabolic diseases and disorders using a composition comprising an antigen binding protein specific for the GIPR polypeptide conjugated to a GLP-1 receptor agonist are provided. In various embodiments the metabolic disease or disorder is type 2 diabetes, obesity, dyslipidemia, elevated glucose levels, elevated insulin levels and diabetic nephropathy. In certain embodiments the composition comprises an antibody or functional fragment thereof comprising a cysteine at one or more conjugation site(s) wherein the GLP-1 receptor agonist is conjugated to the antibody or functional fragment thereof through the side-chain of the cysteine residue.



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference A-2124-WOPCT	FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. PCTUS2018/013918	International filing date (day/month/year) 16.01.2018	Priority date (day/month/year) 17.01.2017	
International Patent Classification (IPC) or national classification and IPC INV. A61K39/395			
Applicant Amgen Inc.			
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>7</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ (sent to the applicant and to the International Bureau) a total of <u>43</u> sheets, as follows: ☒ sheets of the description, claims and/or drawings which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions). ☐ sheets containing rectifications, where the decision was made by this Authority not to take them into account because they were not authorized by or notified to this Authority at the time when this Authority began to draw up this report, and any accompanying letters (Rules 66.4bis, 70.2(e), 70.16 and 91.2). ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in the international application as filed, or the superseding sheets were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in item 4 of Box No. I and the Supplemental Box (see Rule 70.16(b)). b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing, in the form of an Annex C/ST.25 text file, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 3ter of Annex C of the Administrative Instructions).			
4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ Box No. II Priority ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability ☐ Box No. IV Lack of unity of invention ☒ Box No. V Reasoned conclusion under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement ☒ Box No. VI Certain documents cited ☐ Box No. VII Certain defects in the international application ☒ Box No. VIII Certain observations on the international application			
Date of submission of the demand 19.11.2018		Date of completion of this report 26.03.2019	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465		Authorized officer Scheffzyk, Irmgard Telephone No. +49 89 2399-8602	



INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2018/013918

Box No. I Basis of the report

1. With regard to the **language**, this report is based on
- ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a) and (b))
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-557 as originally filed

Sequence listings, SEQ ID NO

3309 filed with the letter of 04-12-2018

Claims, Numbers

1-21 as originally filed

Drawings, Sheets

1/40-40/40 filed with the letter of 16-11-2018

- ☒ a sequence listing - see Supplemental Box Relating to Sequence Listing.
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-bis)):
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2018/013918

5. ☐ This report has been established:
- ☐ taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rules 66.1(d-*bis*) and 70.2(e)).
 - ☐ without taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91(Rules 66.4*bis* and 70.2(e)).
6. ☒ With regard to top-up searches (Rules 66.1*ter* and 70.2(f)):
- ☐ A top-up search was carried out by this Authority on (all discovered documents are listed in the Supplemental Box Relating to Top-up Search).
 - ☐ Additional relevant documents have been discovered during the top-up search.
 - ☒ No top-up search was carried out by this Authority because it would serve no useful purpose.
7. ☐ Supplementary international search report(s) from Authority(ies) has/have been received and taken into account in establishing this report (Rule 45bis.8(b) and (c)).

* If item 4 applies, some or all of those sheets may be marked "superseded".

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-21</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-21</u>
Industrial applicability (IA)	Yes: Claims	<u>1-21</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2018/013918

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed:
 - ☒ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13~~ter~~.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search and/or examination:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13~~ter~~.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13~~ter~~.1(b) and Administrative Instructions, Section 713).
 - d. ☒ furnished to this Authority as an amendment* under PCT Article 34 on 16.11.2018:
 - ☒ in the form of an Annex C/ST.25 text file, and preferably identified as "Amended" at the first line of text.
 - ☐ on paper or in the form of an image file.
2. ☒ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

* *If item 4 in Box No. I applies, the sequence listing, which forms part of the basis of the report, may be marked "superseded."*

Item V

Presently claimed subject-matter is deemed to be novel as a composition comprising an antibody or fragment thereof binding to hGIPR and a GLP-1R agonist conjugated to said antibody or functional fragment thereof is not taught in the available prior art.

However, both receptors, i.e. GIPR and GLP-1R are well-known attractive targets in the treatment of type2diabetes (T2DM) and obesity. Thus, GIPR binding antibodies as well as GLP-1R agonists as well as the use thereof to treat obesity/T2DM are described in the prior art (see e.g. Ravn et al. (D1) Al-Sabah, (D2) (see e.g. abstract) or McLean et al. (D3)). Thus, in view of the prior art the problem underlying present application can be seen in the provision of further GIPR/GLP-1 regulators suitable to treat obesity or T2DM. This problem apparently was solved by providing presently claimed conjugates wherein known GLP-1 receptor agonists (see e.g. D2, page 19) and antibodies binding to hGIPR are combined using methods well-known in the art (see e.g. Schumacher et al.(D4) or Behrens et al. (D5)). However, the combination of (known) compounds for the same purpose cannot be considered to be inventive.

Concerning claims directed to specific sequences it is noted that antibodies containing these sequences seem to be novel. However, taking D1 as closest prior art the provision of further GIPR binding antibodies by using routine methods cannot be considered to be inventive either.

Item VI

In case presently claimed priority date is invalid WO2017112824 would be relevant for the assessment of inventive step of presently claimed subject-matter.

Item VIII

1). The term "wherein said antibody or functional fragment thereof is an antibody (or fragment thereof)" used for instance in claims 12,13,14,15 renders the scope of claims containing said expression unclear.

- 2). It is noted that antibodies must at least be characterised by its 6 CDRs.

- 3). In case present application is pursued as European patent application claim 21 would not be patentable relating to a medical treatment.

European Patent Office

**Bob-van-Bentham-Platz 1
80469 München**

Ihr Zeichen / Your Ref.

Unser Zeichen / Our Ref.

Datum / Date

PCT120852HVMGkry

November 16, 2018

To EPO acting as International Preliminary Examining Authority

**International Patent Application PCT/US2018/013918
Applicant: Amgen Inc.**

Letter accompanying the Demand for International Preliminary Examination

Amendment Under Article 34 Of The Patent Cooperation Treaty

This is in response to the Invitation to Correct Defects in the International Application, mailed 21 March 2018, for the above-referenced application as filed.

At the invitation of the Office, Applicants enclose replacement sheets of figures 1 through 30 (40 Sheets total) for incorporation into the International Application.

Additionally, Applicants furnish a substitute nucleotide and/or amino acid sequence listing in computer readable form (CRF), and have corrected errors found in: 1) the length of the title found at <120> was greater than 74 characters and has been corrected; 2) Invalid/missing amino acid numbering found in SEQ ID NO:3251 was inserted; 3) Numeric identifier <150> "Prior Application Number" on page one and numeric identifier <151> "Prior Application Filing Date" were missing and have been inserted; and 4) Missing numeric identifier <150> is missing the PCT application number and this has been inserted. This revised CRF of the sequence listing is also accompanied by a statement that the sequence listing does not go beyond the disclosure in the application as filed and includes no new matter. By way of this amendment, Applicant directs the Office to incorporate this substitute "txt" version of the sequence listing into the application as filed.

MÜNCHEN

Patentanwälte
European Patent Attorneys
Hans Hügers
Thomas Schuster
Dr. Klara Goldbach
Martin Aulenanger, LL.M., MM
Dr. Heike Vogelsang-Wenke
Reinhard Knauer
Dietmar Kuhl
Dr. Franz-Josef Zimmer
Betina K. Reichelt
Dr. Anton K. Pfau
Dr. Udo Weigelt, LL.M.
Rainer Bertram
Jens C. Koch, M.S. (J of PA)
Bernd Rothaemel
Thomas W. Laubenthal, LL.M.
Dr. Andreas Koyser
Dr. Jens Hammer
Dr. Thomas Eickelkamp
Dr. Peter Miltényi²
Dr. Moritz Höfle, LL.M.
Gero Maatz-Jansen
Michael Heise
Christian Meisinger
Dr. Martin Ahr
Dr. Wolfgang Naubeck
Steven M. Zeman, Ph.D.
André Nickel
Felix Kahr
Dr. Alexander Stumvoll, LL.M.
Dr. Stefano Marchini³
Dr. Thomas Kronberger
Yilin Jin
Dr. Georg Seisenberger
Dr. Olivia Nemethova, LL.M.
Dr. Rainer Plaggenborg
Victor Lopes Aguiar
Dr. Sabine Koch
Wolfram Thomas
Dr. Markus Grammel

Rechtsanwälte
Attorneys-at-Law
Dr. Ulrich Blumenröder, LL.M.
Prof. Dr. Maximilian Kinkeldey, LL.M.⁴
Dr. Karsten Brandt
Anja Franke, LL.M.
Ute Stephan
Dr. Bernd Allekotte, LL.M.⁵
Dr. Elvira Bertram, LL.M.
Babett Ertle
Christine Neuhierl
Sabine Brandstätter
Cornelia Schmitt
Petra Lübbe
Dr. Holger Gauss
Dr. Nicolás Schmitz
Marina Schlumberger
Kirsten Hammerstingl
Sebastian Crotten, LL.M.
Jennifer Rosenhäger, LL.M.
Mark Peters, LL.M.
Dr. Nicola Busch
Julia Bittner, LL.M.
Sebastian Ochs
Philipp Strommer
Jan Rether
Karin Lochner

BERLIN

Patentanwälte
European Patent Attorneys
Dr. Patrick P. Erk, M.S. (MIT)
Dr. Svenja Sethmann
Tino Rumpold

KÖLN

Patentanwälte
European Patent Attorneys
Dr. Martin Dropmann

PARIS⁶

Conseil en Propriété Industrielle
European Patent Attorney
Dr. Wolfgang Neubeck

OF COUNSEL

Patentanwälte
European Patent Attorneys
Gottfried Klitzsch

Rechtsanwälte
Attorneys-at-Law
Dr. Helmut Eichmann
Gerhard Barth

Grünecker Patent- und Rechtsanwälte PartG mbB

Leopoldstr. 4
80802 München
Germany

Tel. +49 (0) 89 21 23 50
Fax +49 (0) 89 22 02 87
Mail info@grünecker.de

Amtsgericht: München
Partnerschaftsregister:
PR 1397

Deutsche Bank München
SWIFT / BIC-code: DEUT DE 33
IBAN: DE47 7007 0010 0175 173400

¹ auch/also: Mediator ² auch/also: Agente de la Propriété Industrielle (Espagne) ³ auch/also: Consulente in Brevetti (Italia)

⁴ Professor an der Fachhochschule für angewandtes Management ⁵ auch/also: Attorney-at-Law New York ⁶ in Kooperation/in cooperation

Applicant also provides both a marked-up and a clean version of the specification showing corrections made to the brief description of several views of the drawings. In addition, the drawings have been relabeled in the specification under brief description of the drawings. Applicant also has removed the "shading" found on pages 50, 129, 157, and 189 which tables contain text that has insufficient clarity and contrast and makes the papers difficult to read if reproduced.



Dr. H. Vogelsang-Wenke
- Patent Attorney -

Grünecker Patent- und Rechtsanwälte PartG mbB Leopoldstr. 4 80802 München Germany

European Patent Office

Bob-van-Bentham-Platz 1
80469 München

Ihr Zeichen / Your Ref:

Unser Zeichen / Our Ref:

Datum / Date

PCT120852HVMGkry

November 16, 2018

To EPO acting as International Preliminary Examining Authority

International Patent Application PCT/US2018/013918

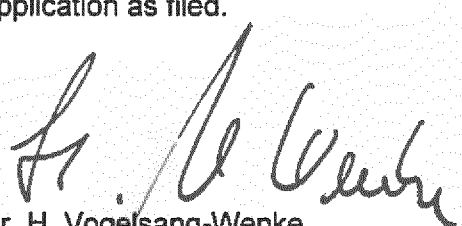
Applicant: Amgen Inc.

Letter accompanying the Demand for International Preliminary Examination

Sequence Listing Statement

Applicant hereby states that the Sequence Listing information recorded in computer readable form (CRF) is identical to the written sequence listing.

Applicants also state that the Sequence Listing submitted herewith does not include any new matter which goes beyond the disclosure of the international application as filed.


Dr. H. Vogelsang-Wenke
- Patent Attorney -

MÜNCHEN

Patentanwälte
European Patent Attorneys
Hans Hilgers
Thomas Schuster
Dr. Klara Goldbach
Martin Aufenanger, LL.M., MM.¹
Dr. Heiko Vogelsang-Wenke
Reinhard Knauer
Dietmar Kuhl
Dr. Franz-Josef Zimmer
Bettina K. Reichelt
Dr. Anton K. Plau
Dr. Udo Weigelt, LL.M.
Rainer Bertram
Jens C. Koch, M.S. (J of PA)
Bernd Rothaemel
Thomas W. Laubenthal, LL.M.
Dr. Andreas Kayser
Dr. Jens Hammer
Dr. Thomas Eickelkamp
Dr. Peter Miltónyi²
Dr. Montz Höfle, LL.M.
Gero Maatz-Jansen
Michael Heise
Christian Meisinger
Dr. Martin Ahr
Dr. Wolfgang Neuback
Steven M. Zeman, Ph.D.
André Nickel
Felix Kahr
Dr. Alexander Stumvoll, LL.M.
Dr. Stefano Marchini³
Dr. Thomas Kronberger
Yilin Jin
Dr. Georg Seisenberger
Dr. Olivia Nemethova, LL.M.
Dr. Rainer Plaggenborg
Victor Lopes Aguiar
Dr. Sabine Koch
Wolfram Thomas
Dr. Markus Grammel

Rechtsanwälte
Attorneys-at-Law
Dr. Ulrich Blumenröder, LL.M.
Prof. Dr. Maximilian Kinkeldey, LL.M.⁴
Dr. Karsten Brandt
Anja Franke, LL.M.
Ute Stephani
Dr. Bernd Allekotte, LL.M.⁵
Dr. Elvira Bertram, LL.M.
Babett Ertle
Christine Neuhierl
Sabine Brandstätter
Cornelia Schmitt
Petra Lübbo
Dr. Holger Gauss
Dr. Nicolás Schmitz
Marina Schlumberger
Kirsten Hammerstingl
Sebastian Clotten, LL.M.
Jennifer Rosenhäger, LL.M.
Mark Peters, LL.M.
Dr. Nicola Busch
Julia Bittner, LL.M.
Sebastian Ochs
Philipp Strommer
Jan Rether
Karin Lochner

BERLIN

Patentanwälte
European Patent Attorneys
Dr. Patrick P. Erik, M.S. (MIT)
Dr. Svenja Selhmann
Tino Rumpold

KÖLN

Patentanwälte
European Patent Attorneys
Dr. Martin Drogmann

PARIS⁶

Conseil en Propriété Industrielle
European Patent Attorney
Dr. Wolfgang Neuback

OF COUNSEL

Patentanwälte
European Patent Attorneys
Gottfried Kitzsch

Rechtsanwälte
Attorneys-at-Law
Dr. Helmut Eichmann
Gerhard Barth

Grünecker Patent- und Rechtsanwälte PartG mbB

Leopoldstr. 4
80802 München
Germany

Tel. +49 (0) 89 21 23 50
Fax +49 (0) 89 22 02 87
Mail info@grunecker.de

Amtsgericht: München
Partnerschaftsregister:
PR 1397

Deutsche Bank München
SWIFT / BIC-code: DEUT DE MM
IBAN: DE47 7007 0010 0175 173400

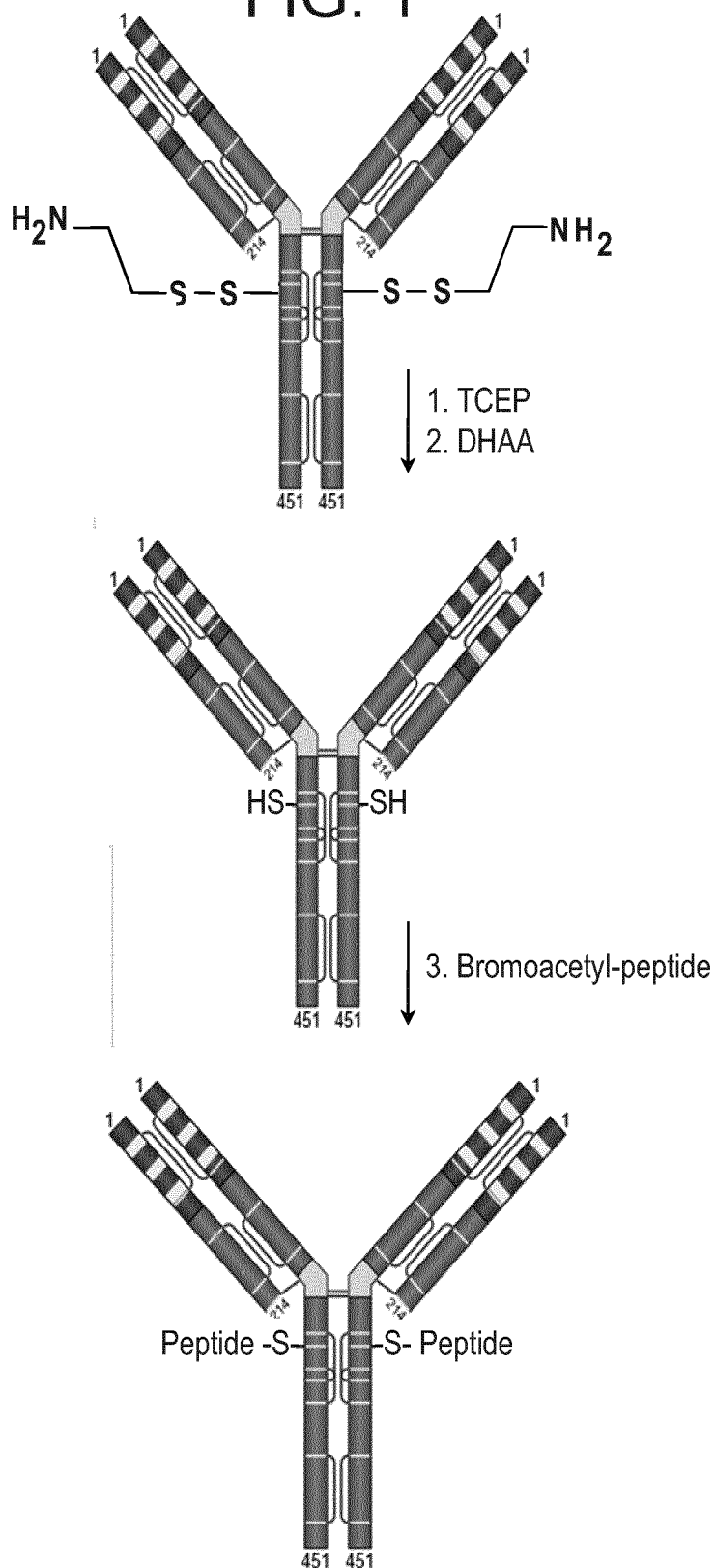
¹ auch/also: Mediator ² auch/also: Agente de la Propiedad Industrial (España) ³ auch/also: Consulente in Brevetti (Italia)

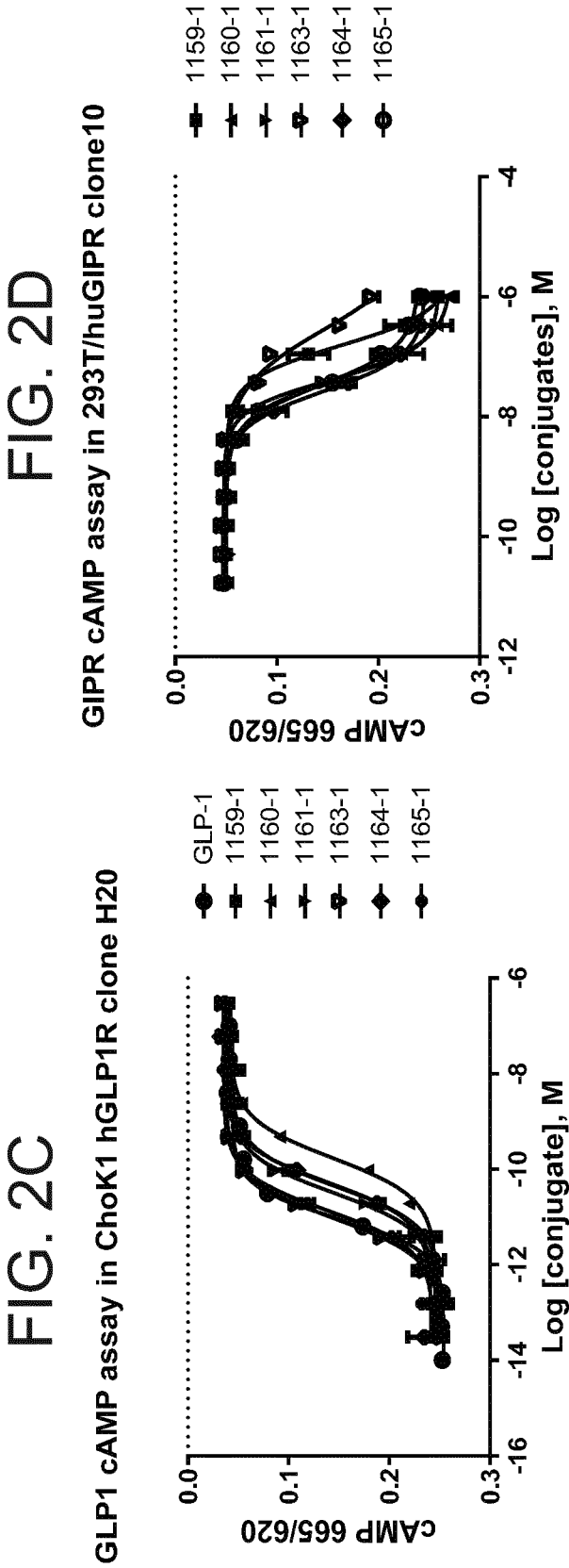
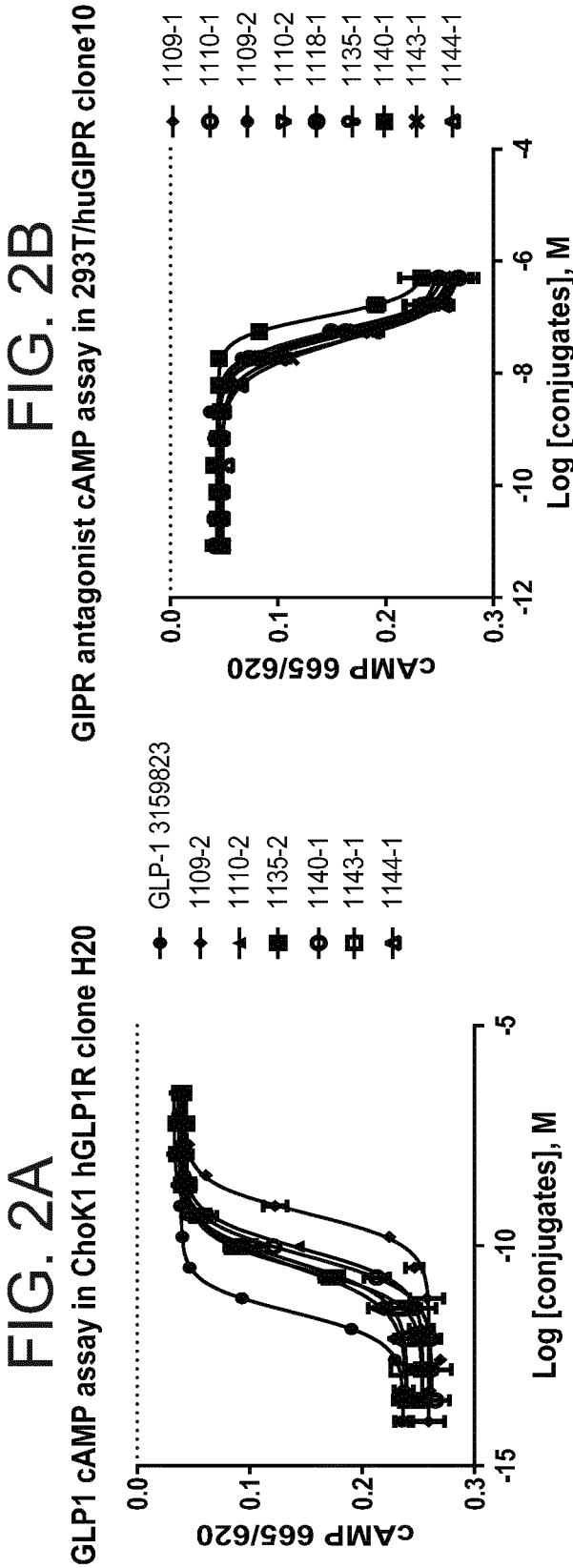
⁴ Professor an der Fachhochschule für angewandtes Management ⁵ auch/also: Attorney at-Law, New York ⁶ in Kooperation/in cooperation

REPLACEMENT SHEET

1/40

FIG. 1





REPLACEMENT SHEET

3/40

FIG. 2E

cAMP assay (GLP-1 agonist mode) in CHOK1 hGLP1R H20

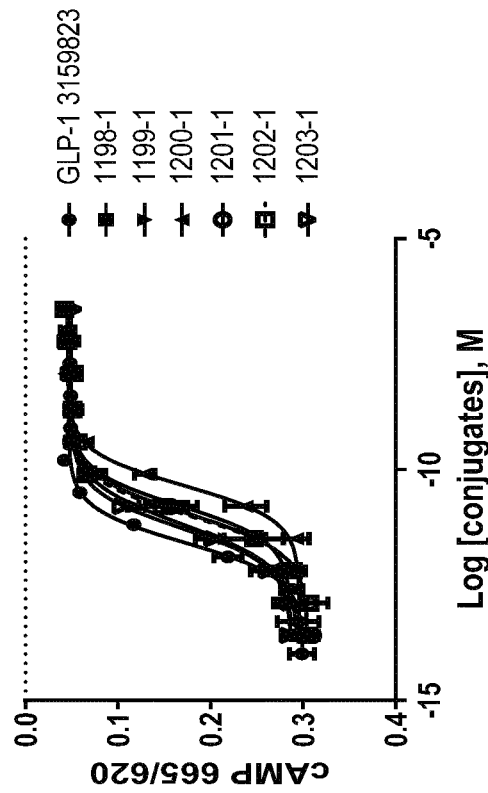


FIG. 2F

cAMP assay (GIPR antagonist mode) in 293T/hGIPR #10

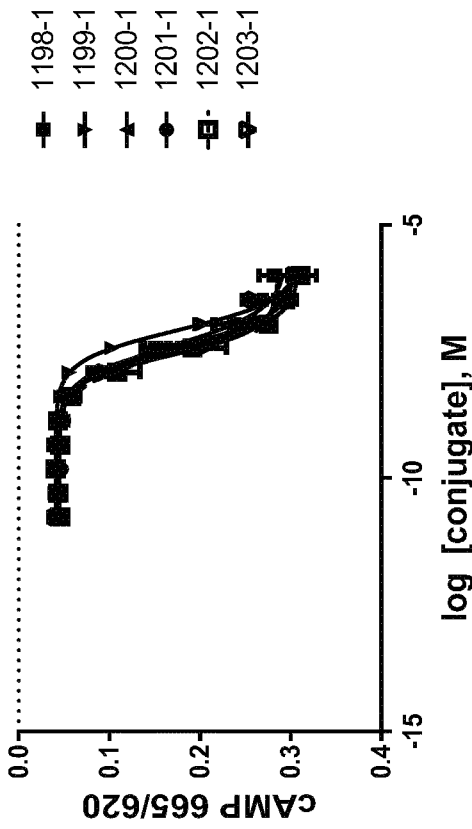


FIG. 2G

cAMP assay (GLP-1 agonist mode) in CHOK1 hGLP1R H20

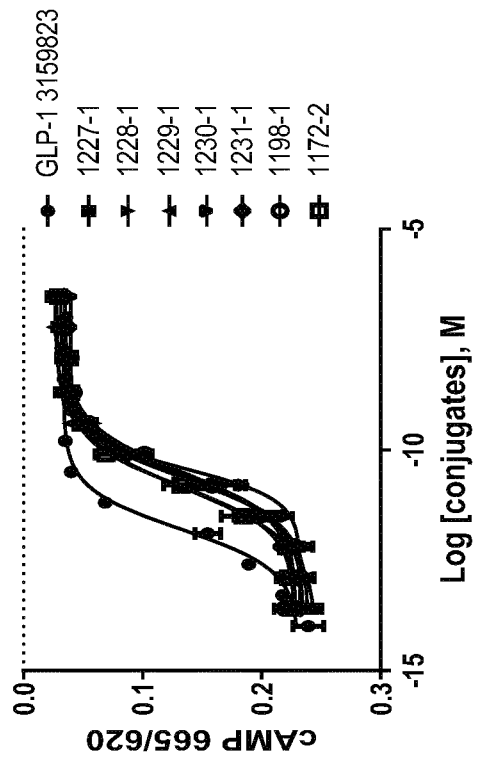
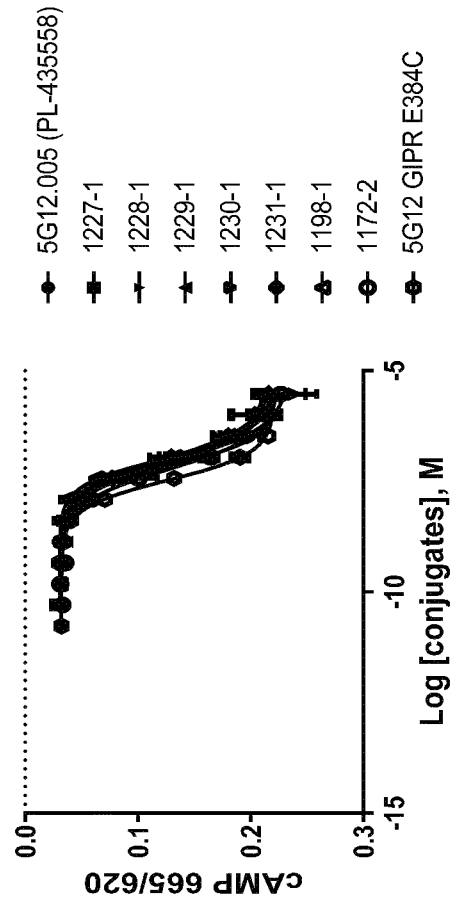


FIG. 2H

cAMP assay (GIPR antagonist mode) in 293T/hGIPR #10



REPLACEMENT SHEET

4/40

FIG. 2I

cAMP assay (GLP-1 agonist mode) in CHOK1 hGLP1R H20

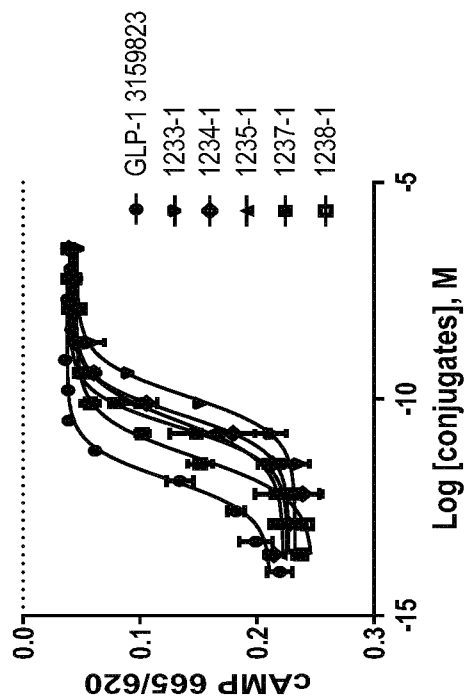


FIG. 2J

cAMP assay (GIPR antagonist mode) in 293T/hGIPR #10

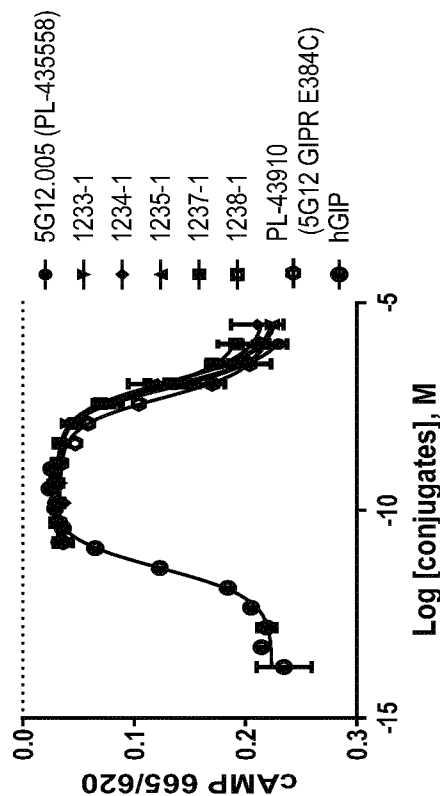


FIG. 2K

cAMP assay (GLP-1 agonist mode) in CHOK1 hGLP1R H20

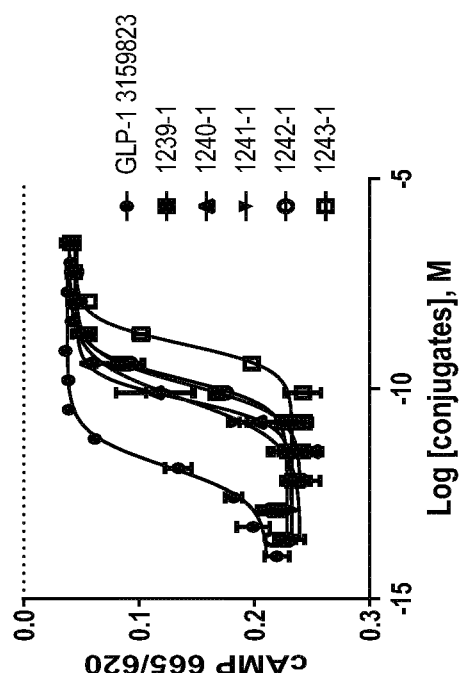
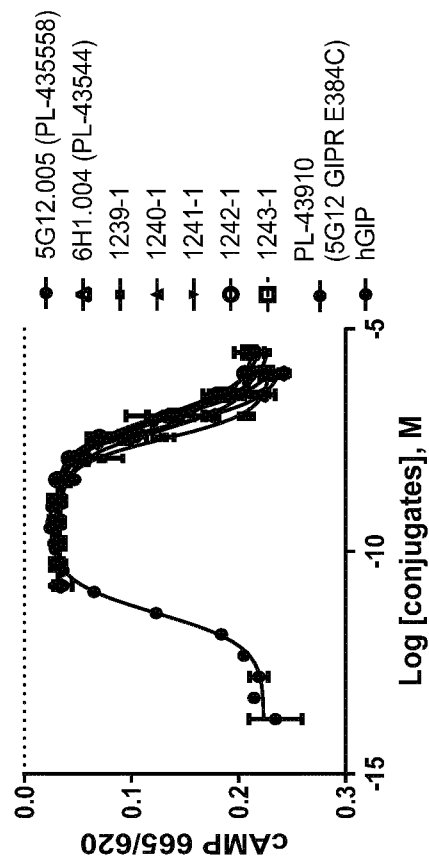


FIG. 2L

cAMP assay (GIPR antagonist mode) in 293T/hGIPR #10



AMENDED SHEET

REPLACEMENT SHEET

5/40

FIG. 2N

cAMP assay (GLP-1 agonist mode) in CHOK1 hGLP1R H20: cAMP assay (GIPR antagonist mode) in 293T/hGIPR #10
Chemical Conjugates on 5G12

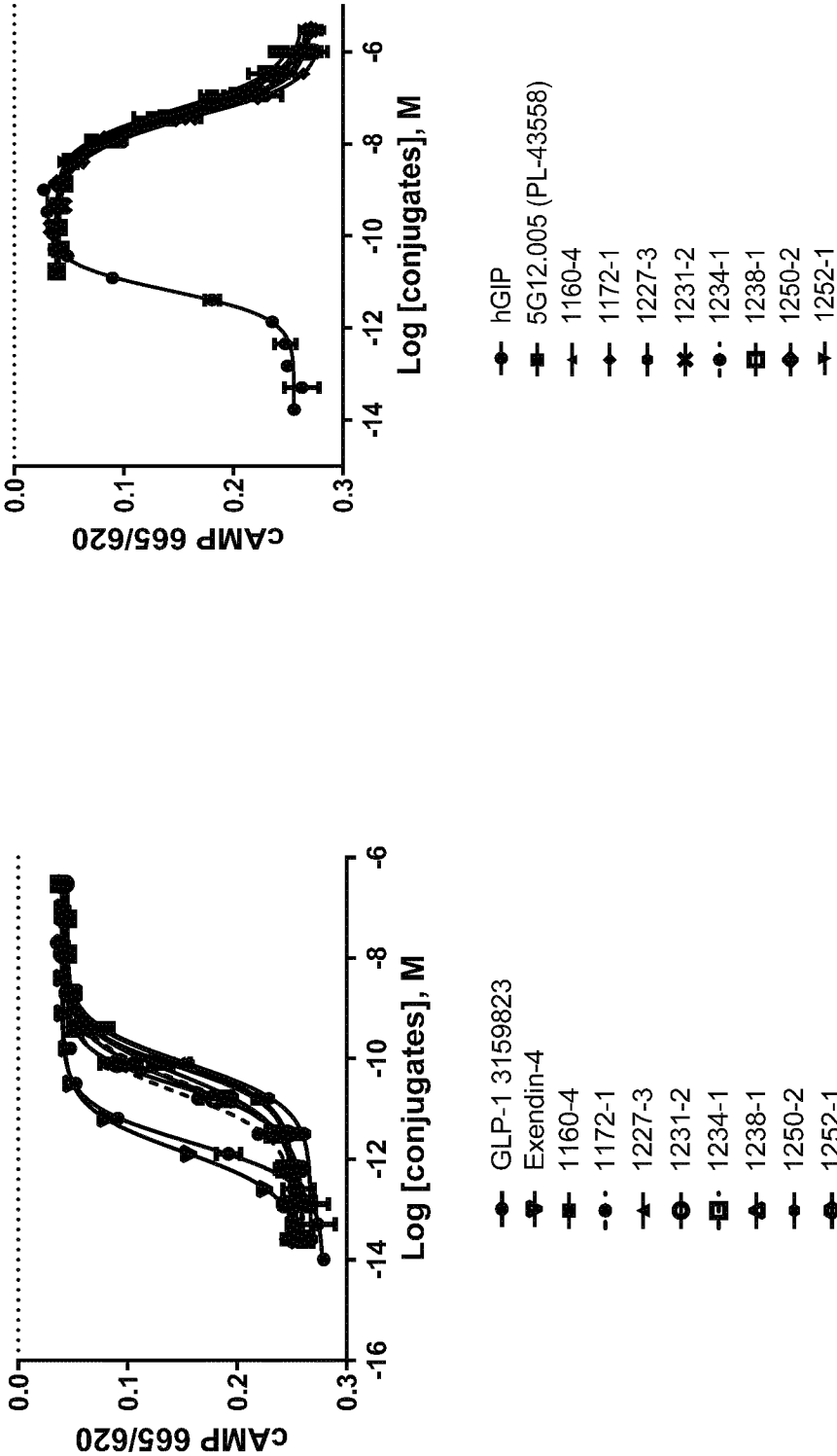
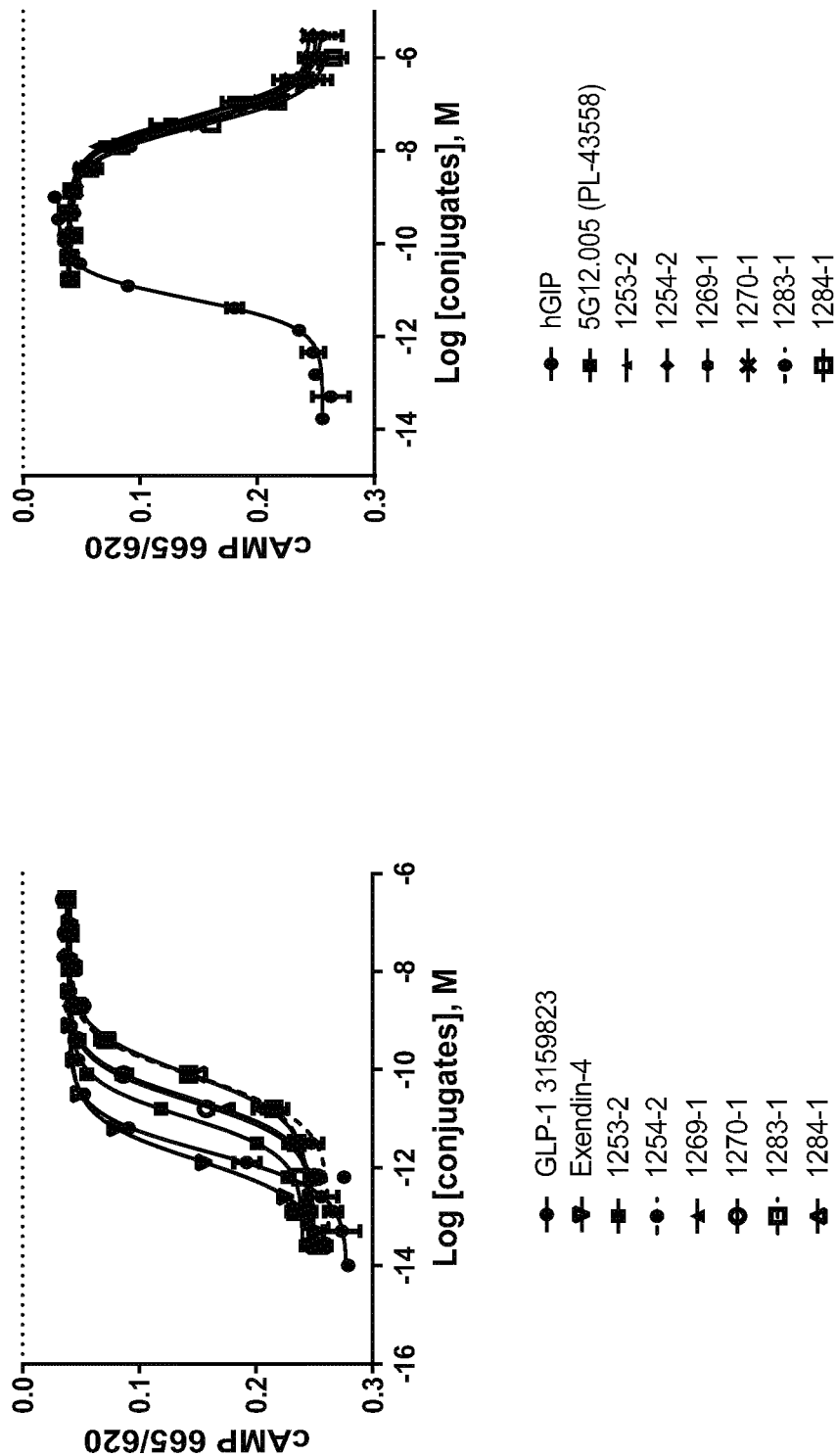


FIG. 2M

REPLACEMENT SHEET

6/40

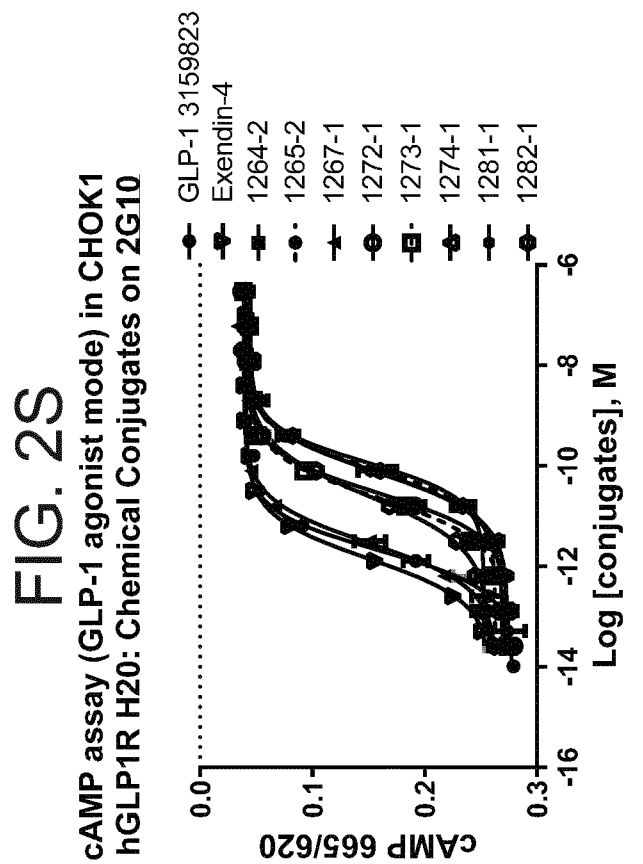
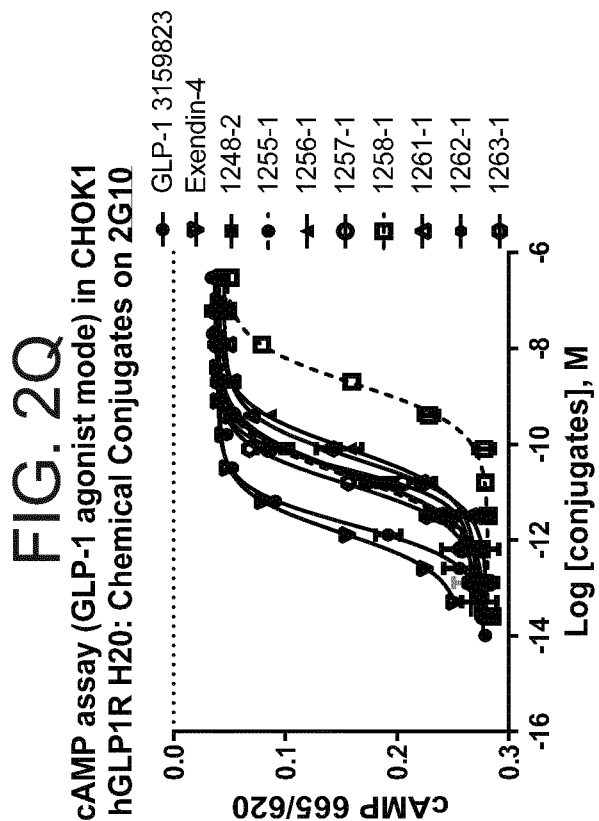
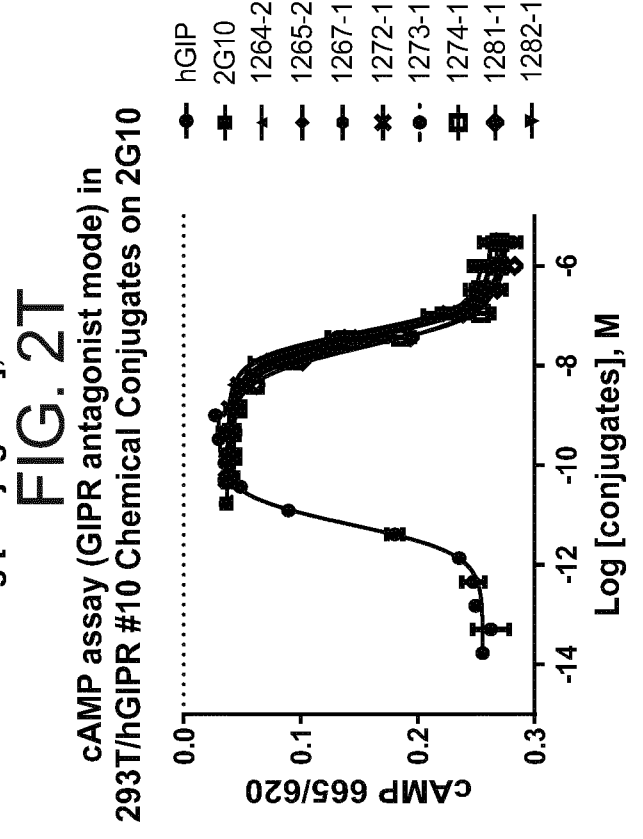
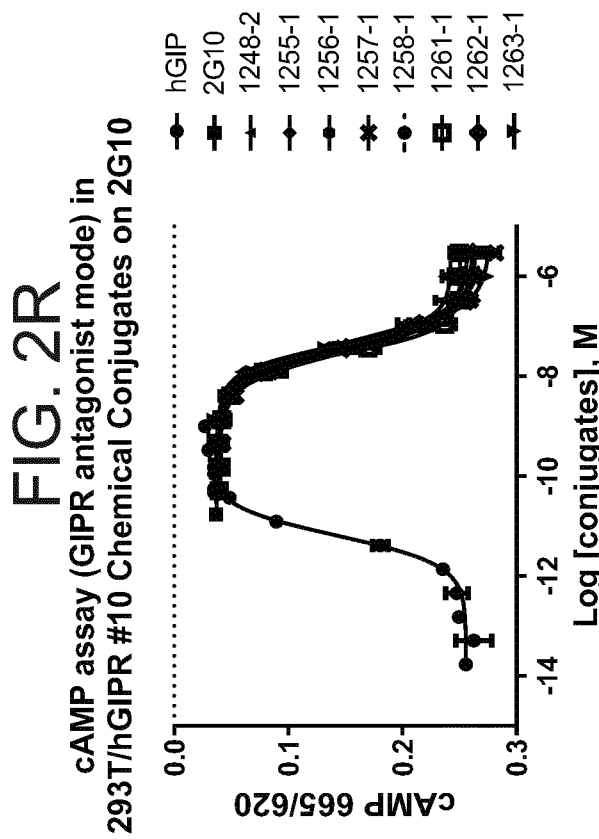
FIG. 20 cAMP assay (GLP-1 agonist mode) in CHOK1 hGLP1R H20: cAMP assay (GIPR antagonist mode) in 293T/hGIPR #10
Chemical Conjugates on 5G12



AMENDED SHEET

REPLACEMENT SHEET

7/40



REPLACEMENT SHEET

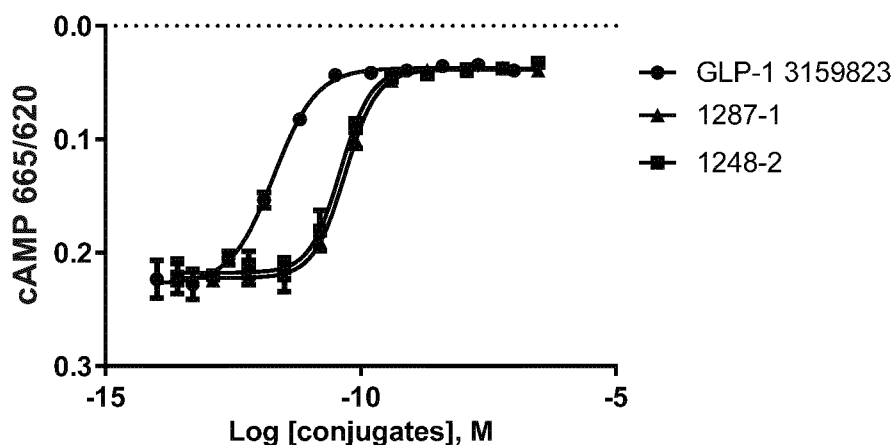
8/40

FIG. 3A

Reg #	Description	Peptide information	CHOK1 hGLP-1R	CHOK1 hGLP-1R/GIPR
1148	3166119-E384C-2G10	[Aib8,22;Gly36]GLP-1(7-37)[(G4S)3(BrAc)]	0.04 nM	0.0008 nM
1187	3166119-E384C-aDNP	[Aib8,22;Gly36]GLP-1(7-37)[(G4S)3(BrAc)]	0.05nM	0.08 nM

FIG. 3B

cAMP assay (GLP-1 agonist mode) in CHOK1 hGLP1R H20:



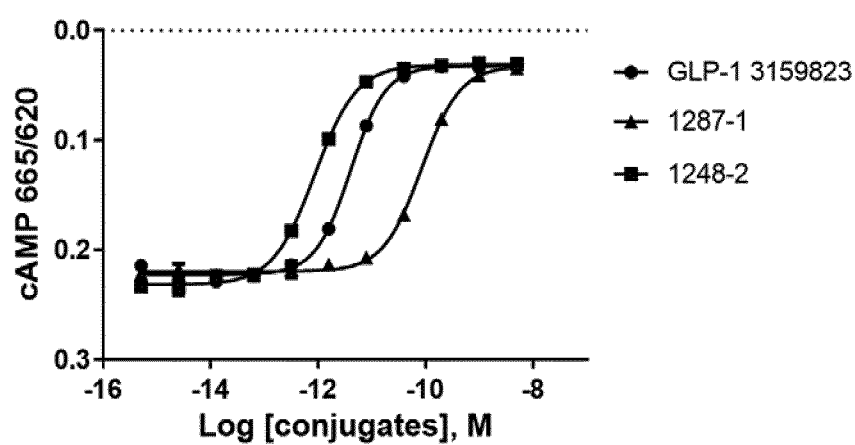
	GLP-1 3159823	1287-1	1248-2
EC50	1.990e-012	4.963e-011	4.010e-011

REPLACEMENT SHEET

9/40

FIG. 3C

cAMP assay (GLP-1 agonist mode) in CHOK1 hGLP1R/hGIPR M1 :



	GLP-1 3159823	1287-1	1248-2
EC50	4.091e-012	8.573e-011	8.793e-013

REPLACEMENT SHEET

10/40

FIG. 4A

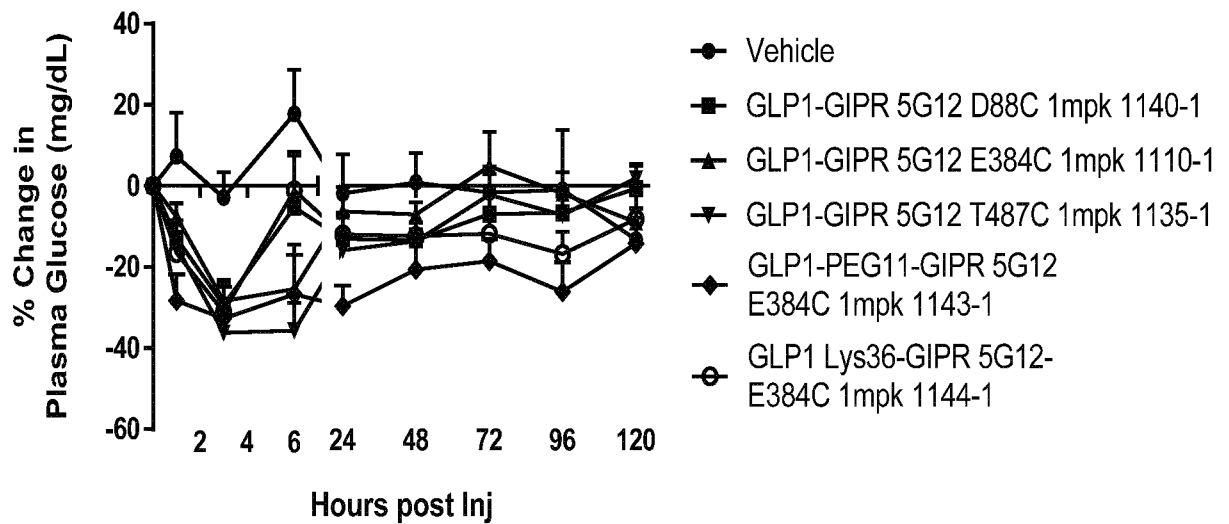
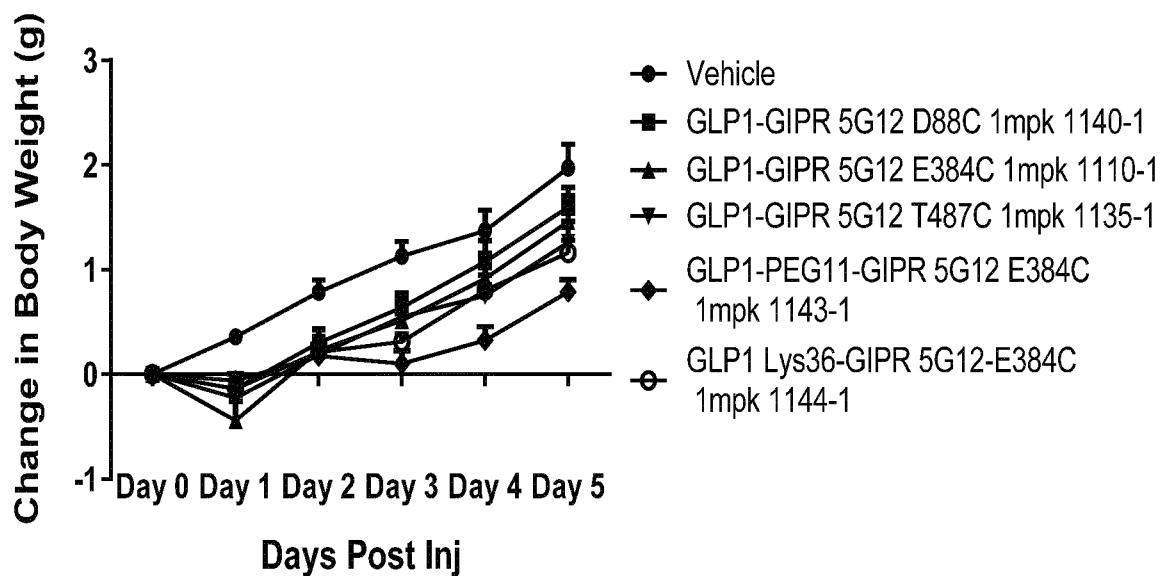


FIG. 4B



REPLACEMENT SHEET

11/40

FIG. 4C

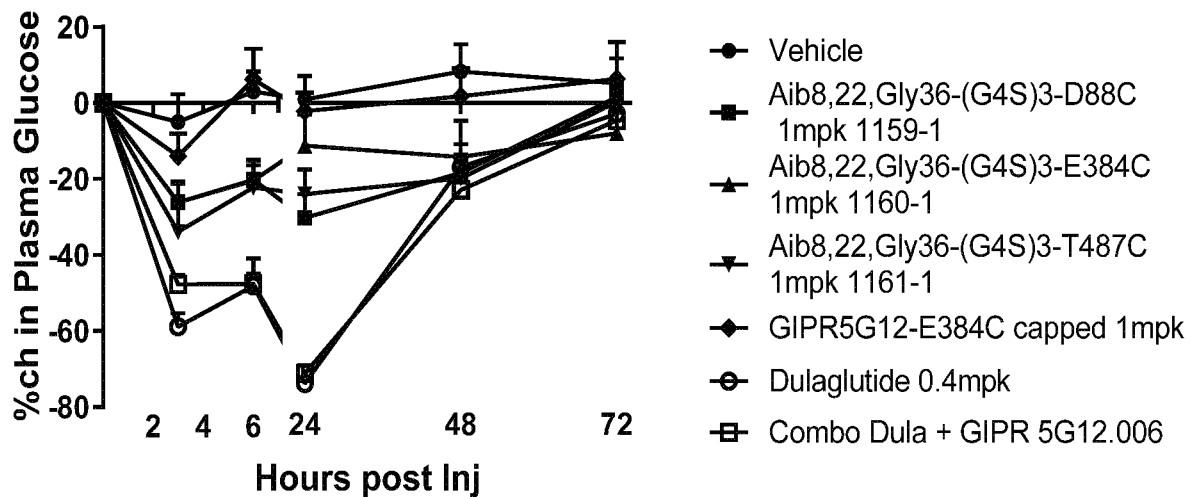
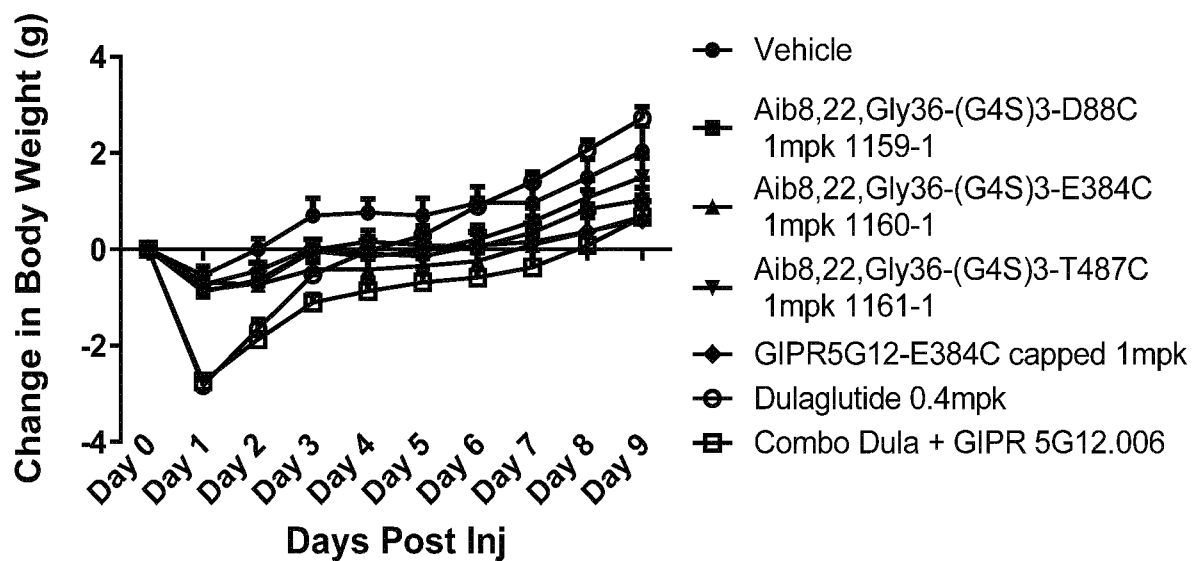


FIG. 4D



REPLACEMENT SHEET

12/40

FIG. 4E

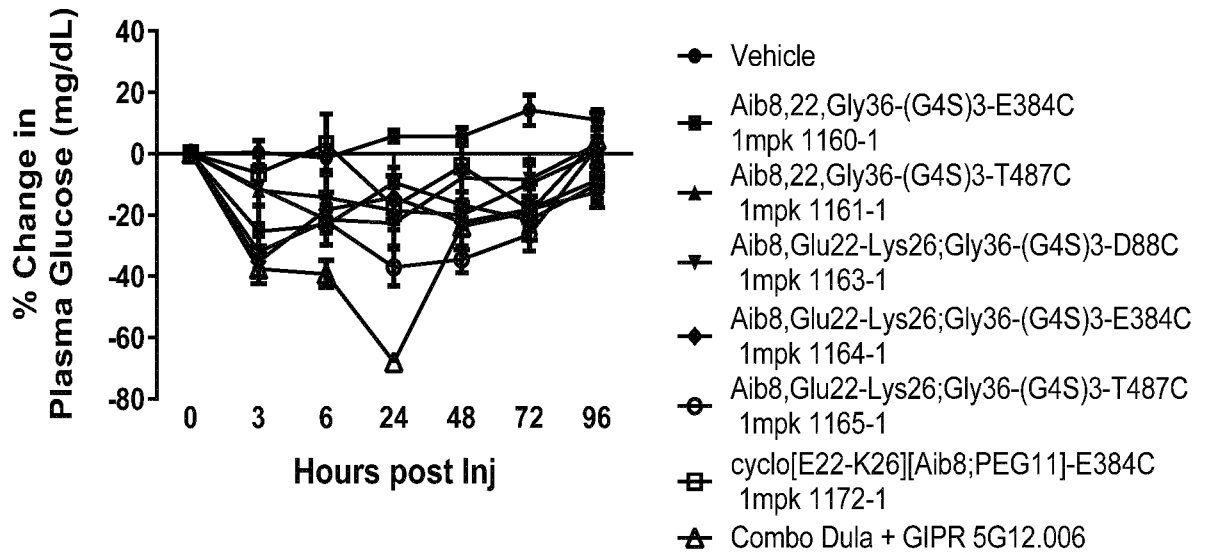
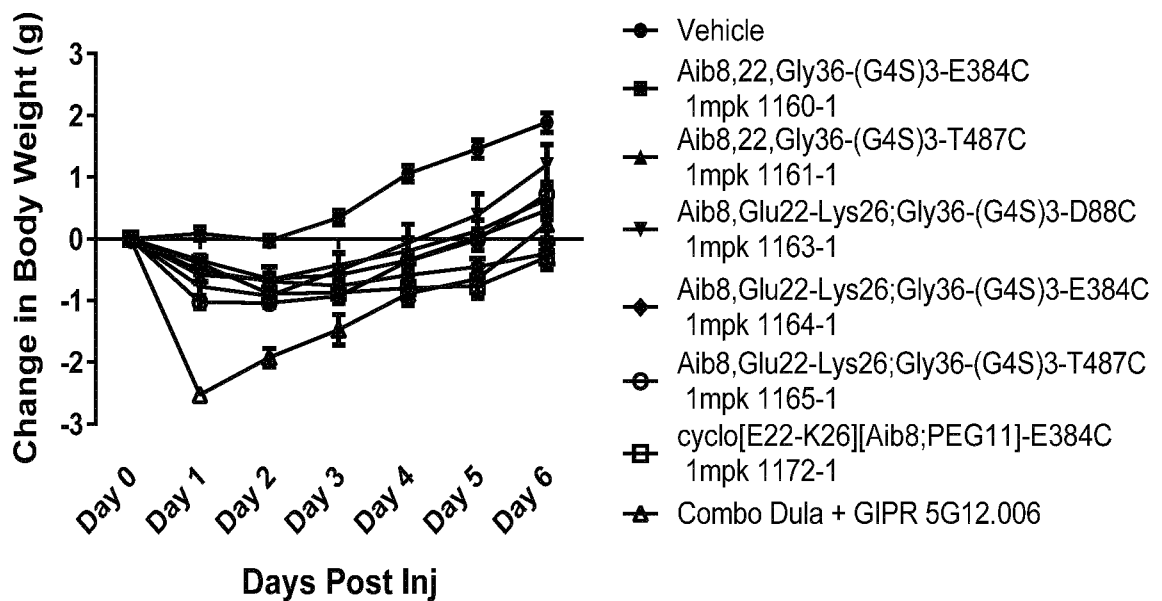


FIG. 4F



REPLACEMENT SHEET

13/40

FIG. 4G

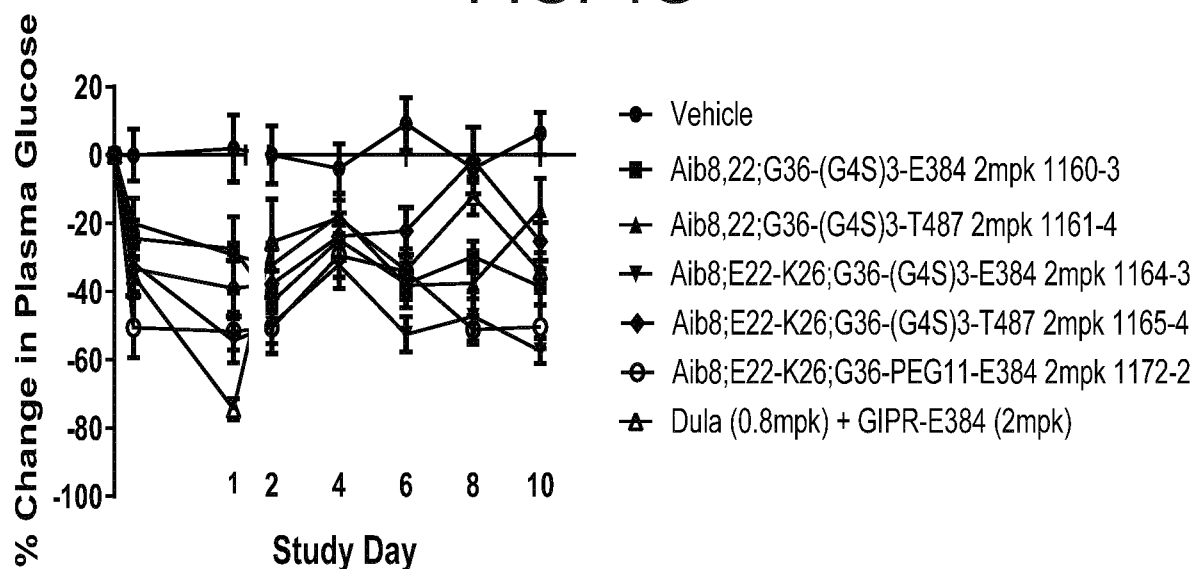
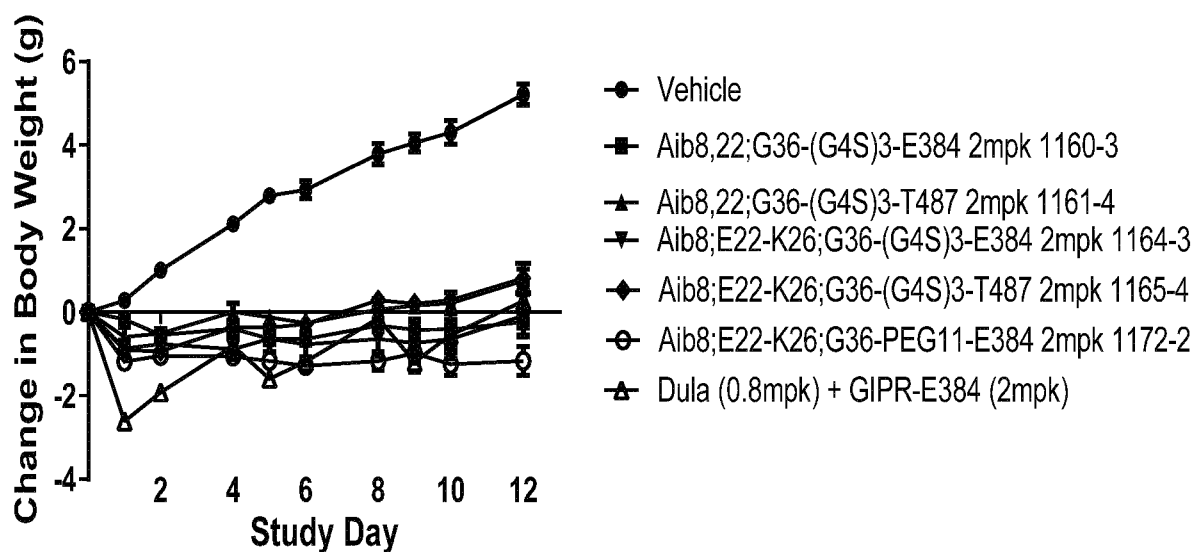


FIG. 4H



REPLACEMENT SHEET

14/40

FIG. 4I

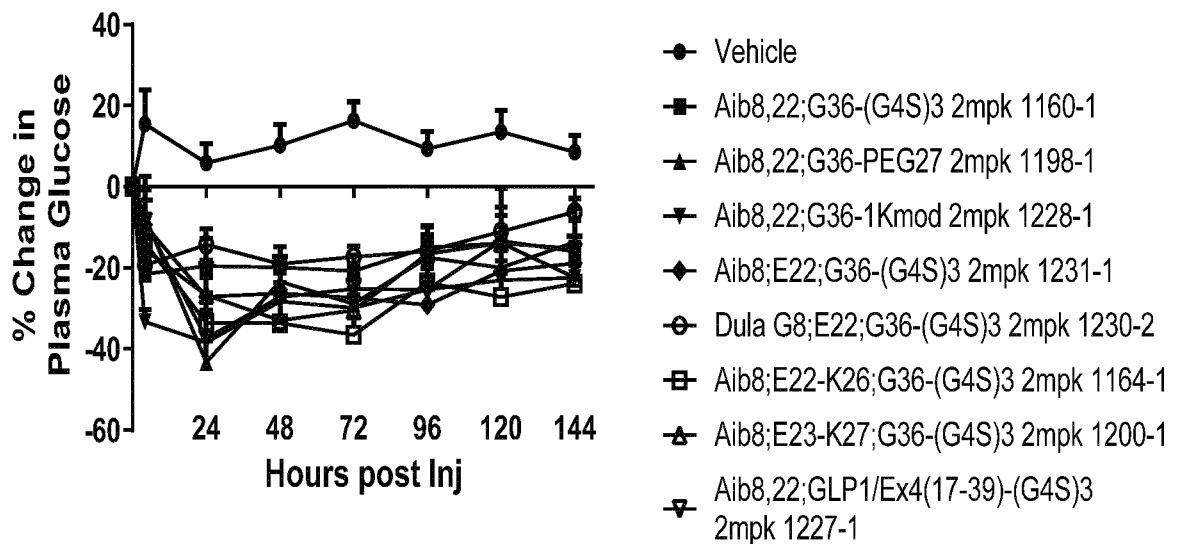
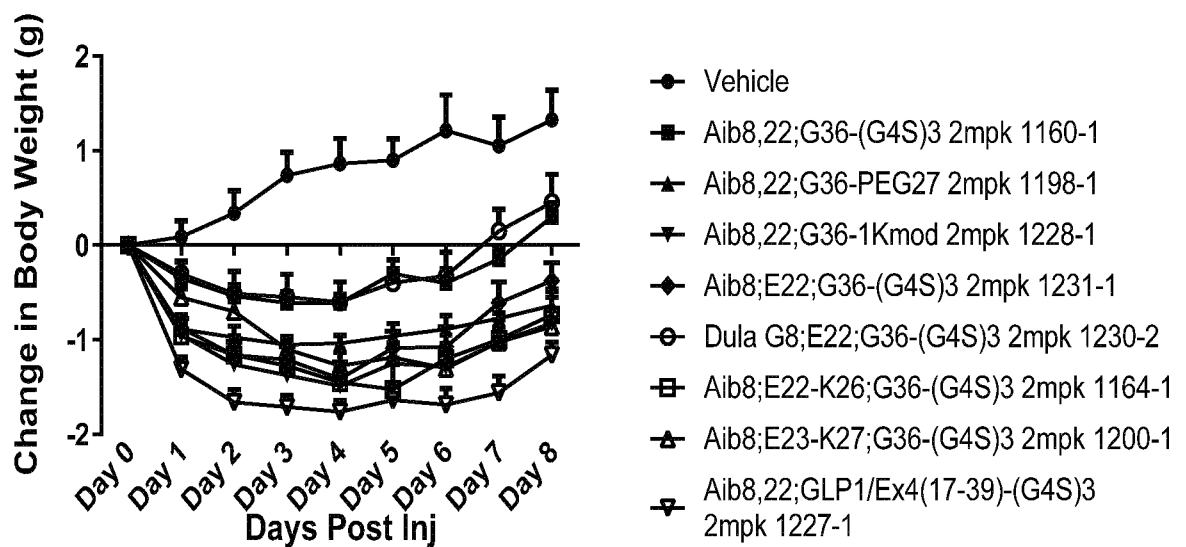


FIG. 4J



REPLACEMENT SHEET

15/40

FIG. 4K

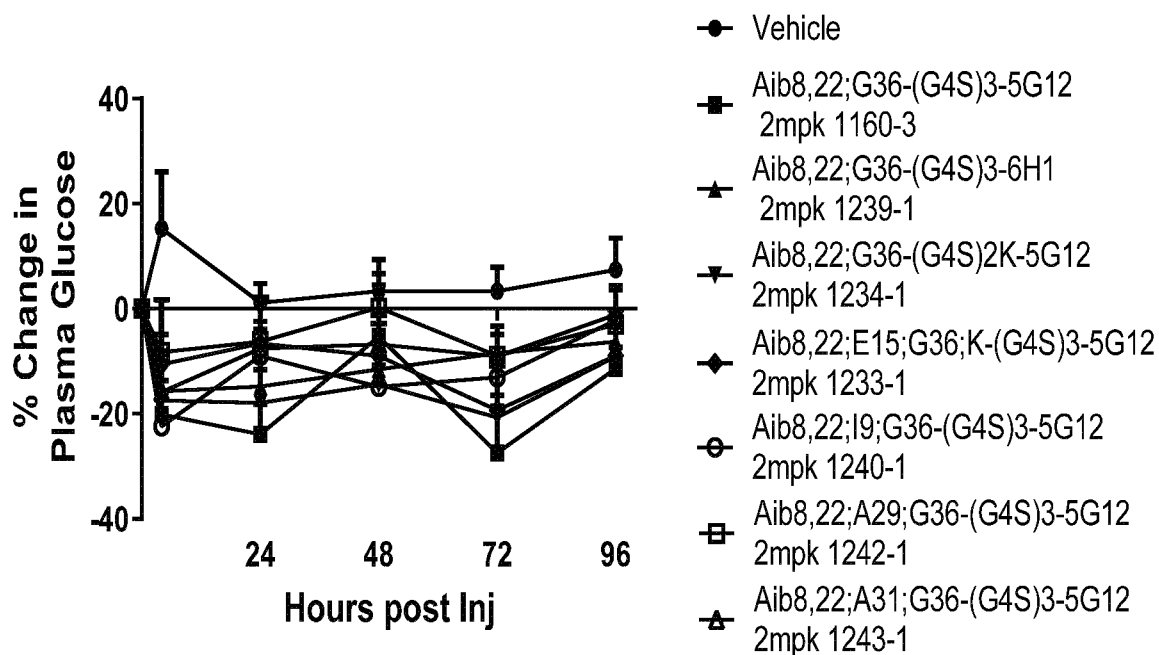
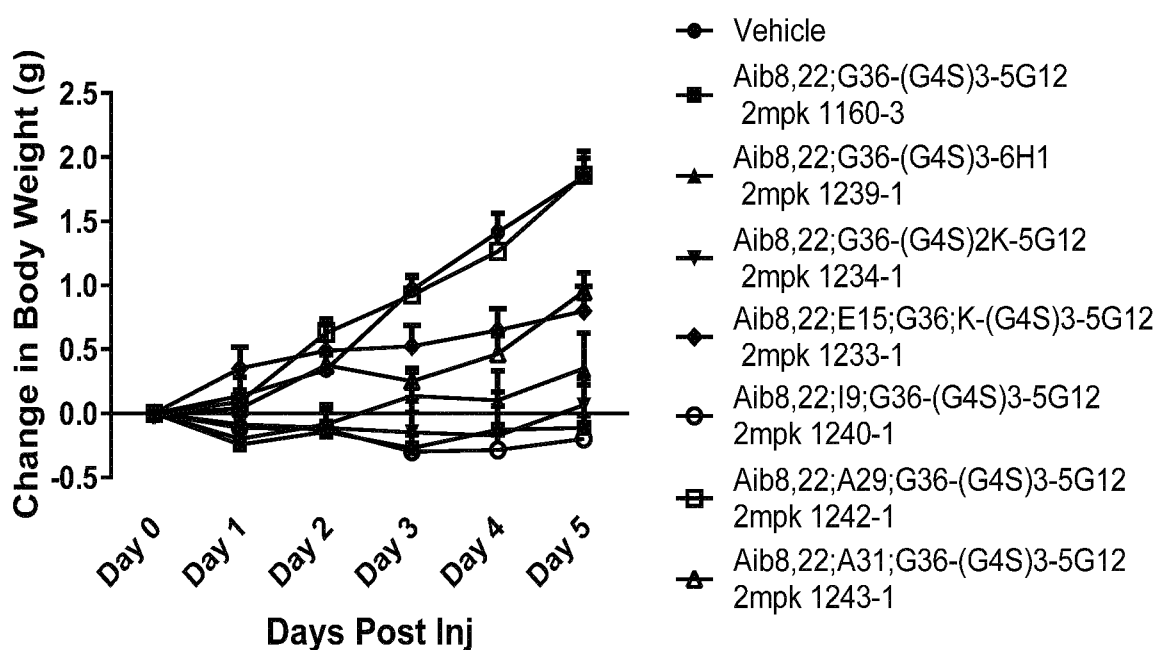


FIG. 4L



REPLACEMENT SHEET

16/40

FIG. 4M

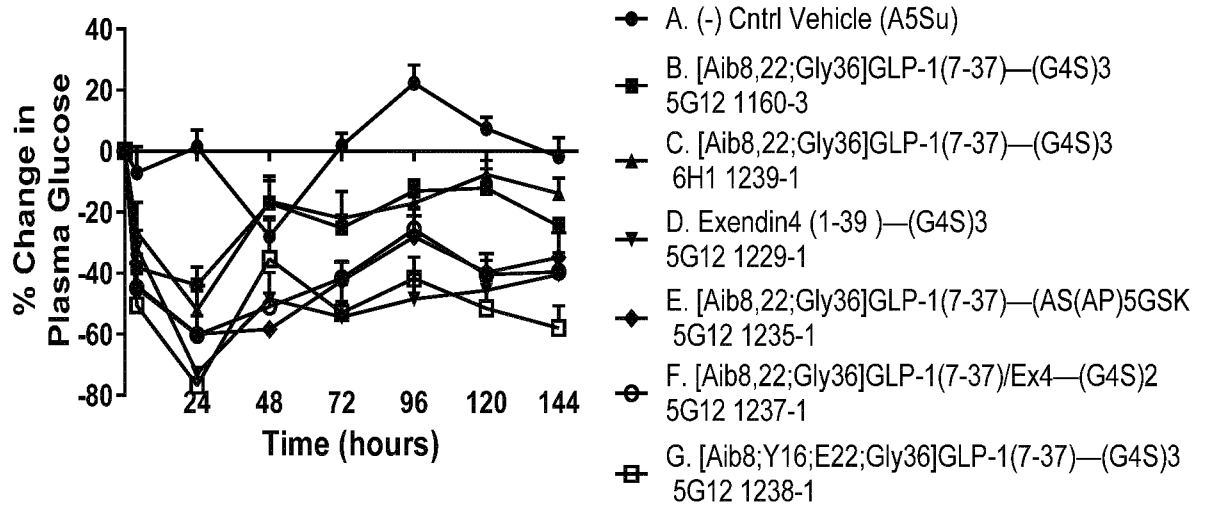
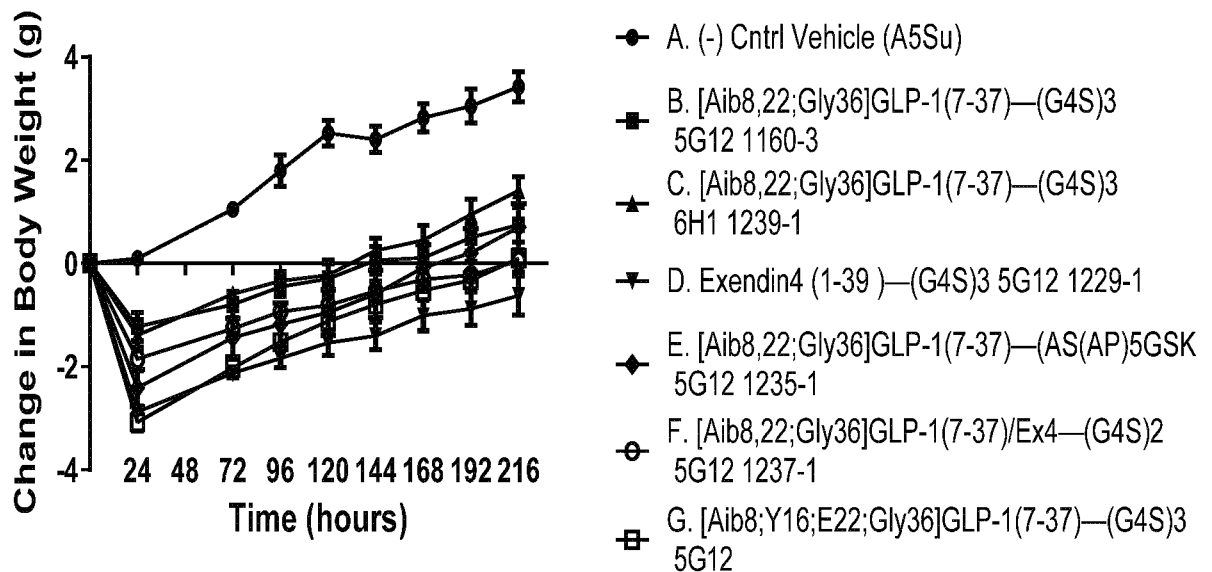


FIG. 4N



REPLACEMENT SHEET

17/40

FIG. 4O

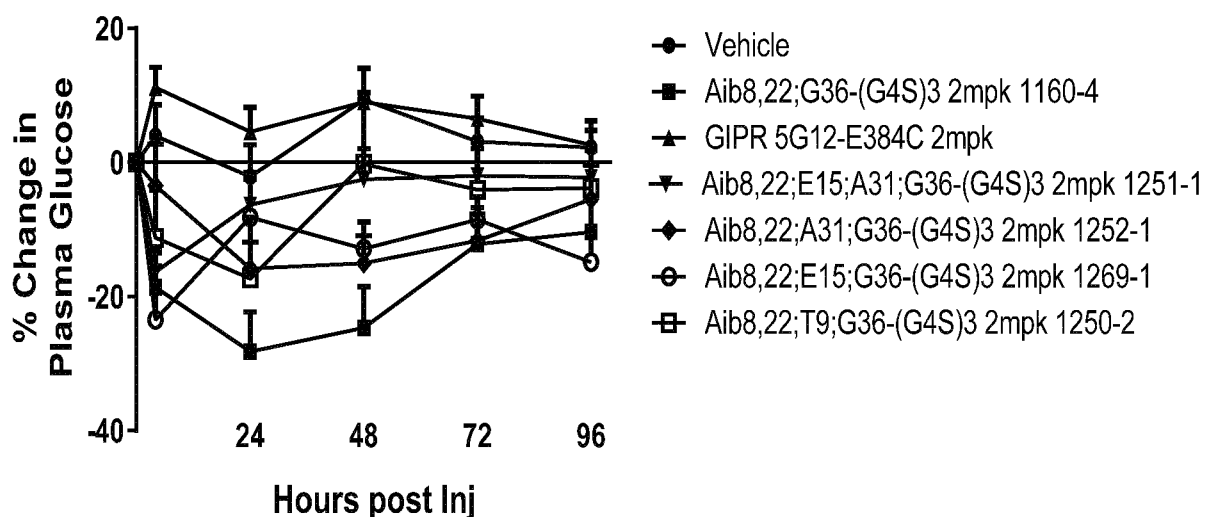
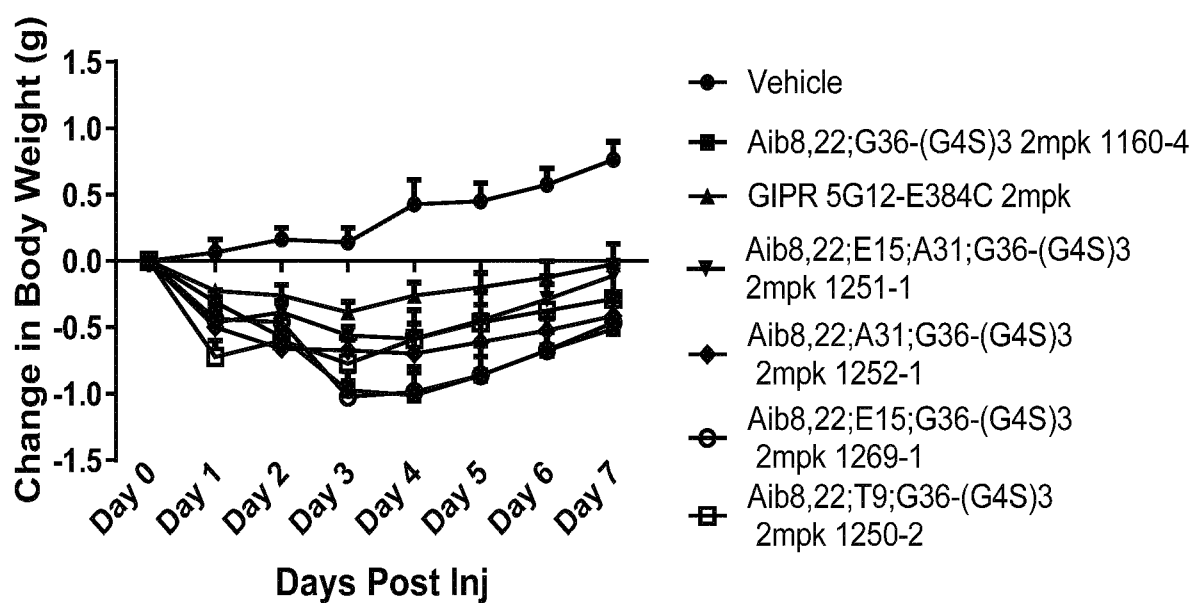


FIG. 4P



REPLACEMENT SHEET

18/40

FIG. 4Q

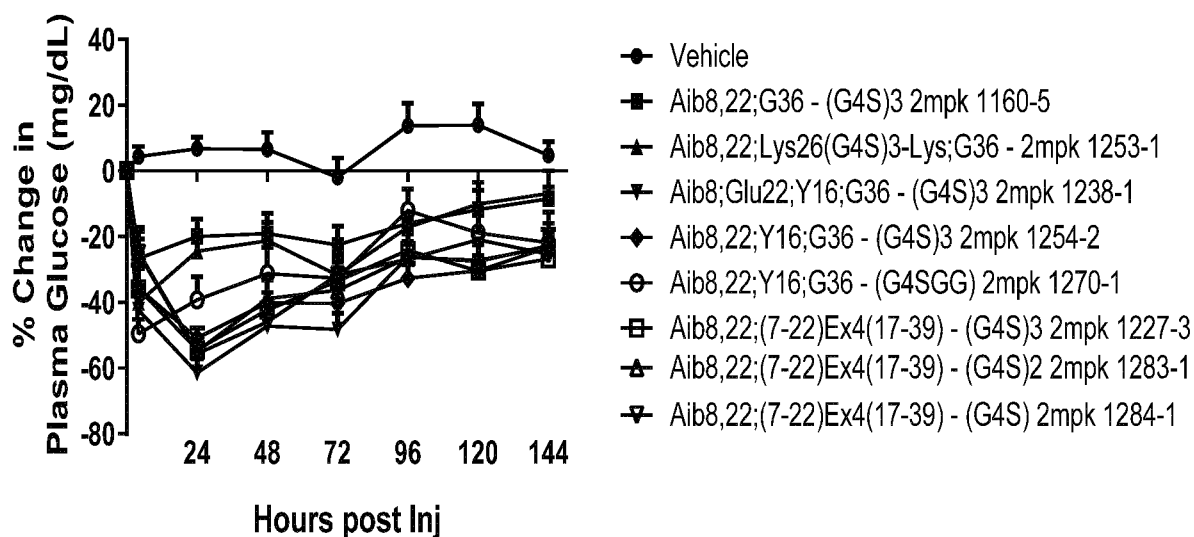
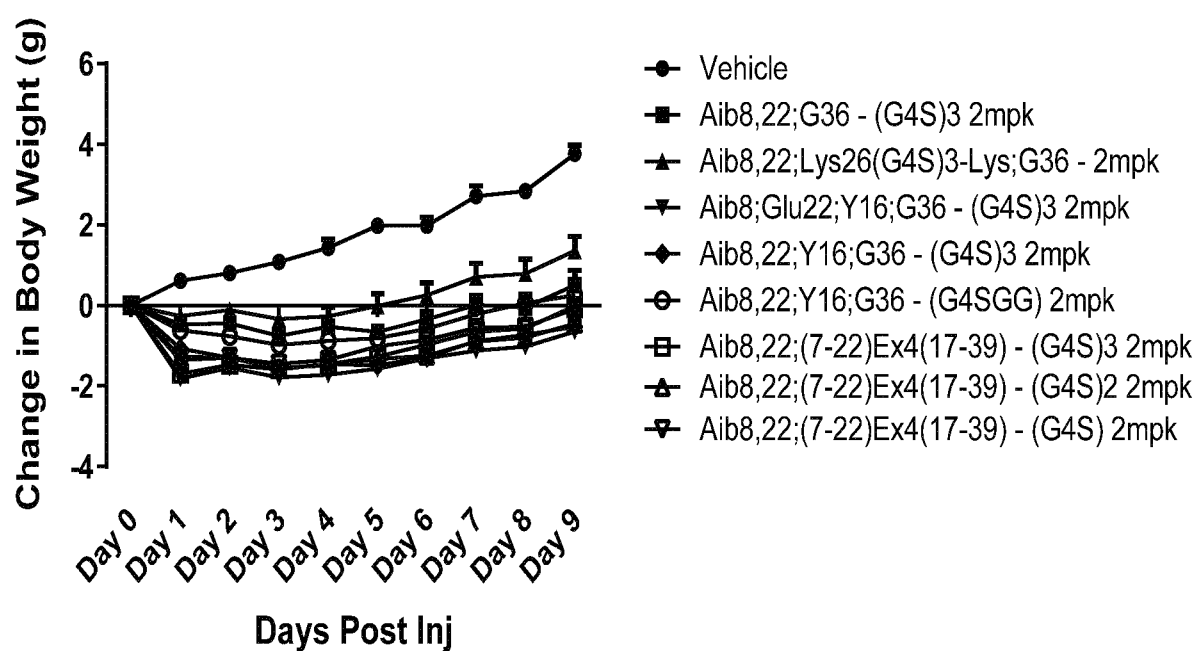


FIG. 4R



REPLACEMENT SHEET

19/40

FIG. 5A

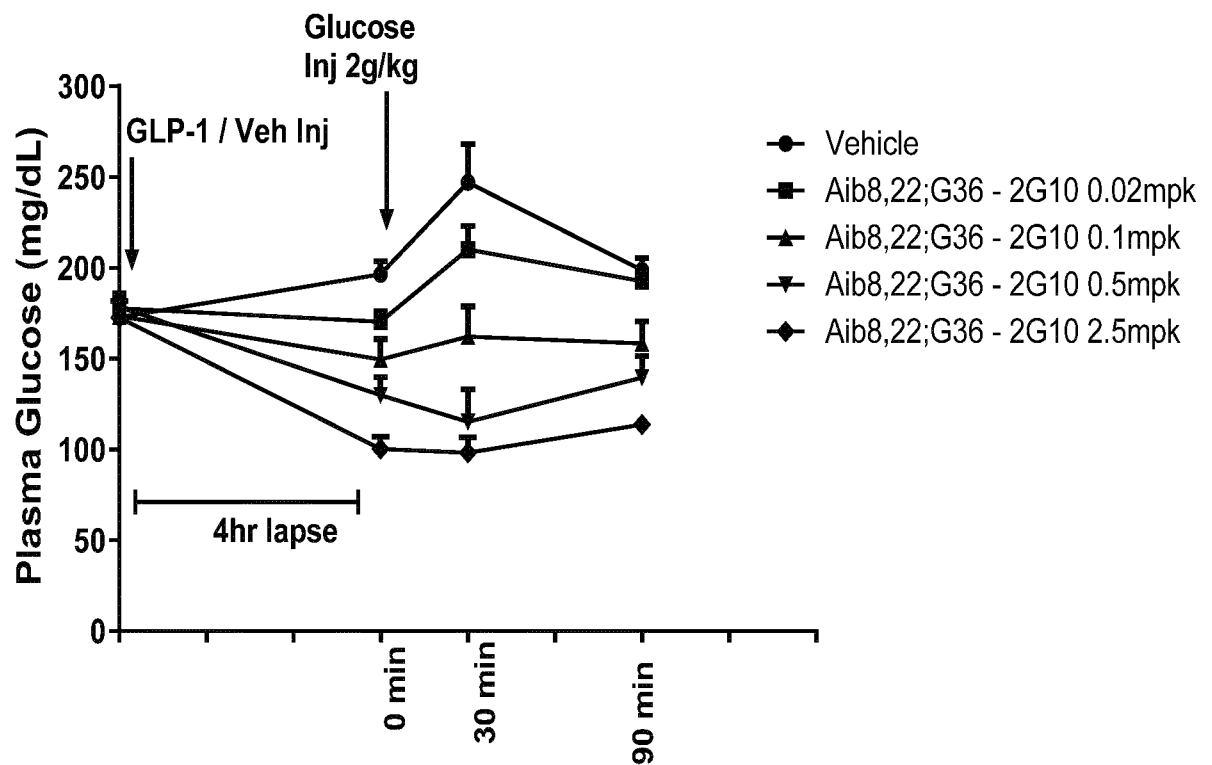
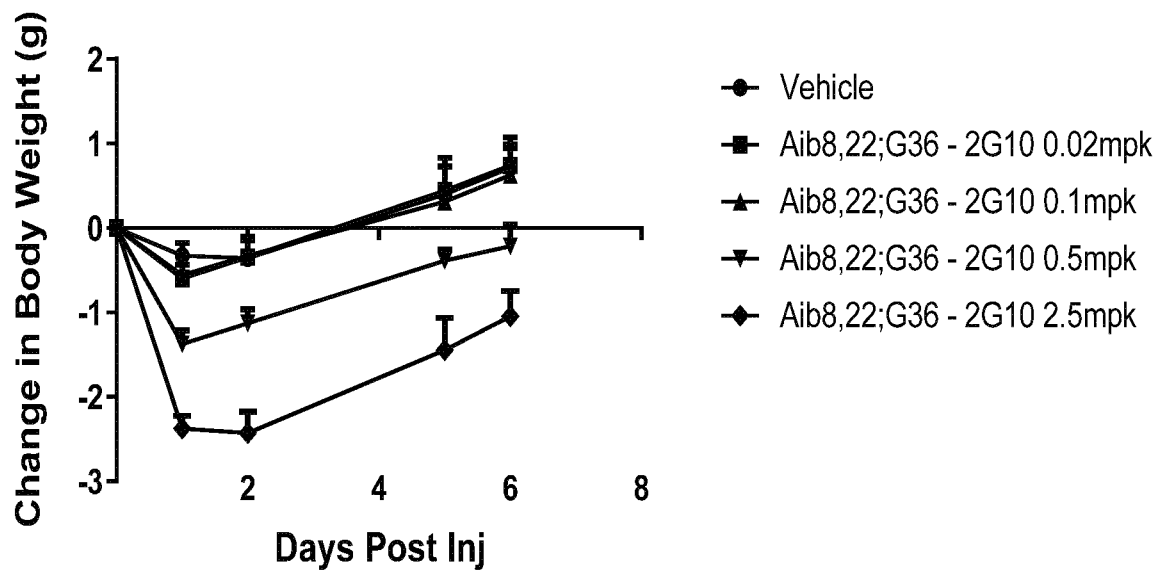


FIG. 5B



REPLACEMENT SHEET

20/40

FIG. 5C

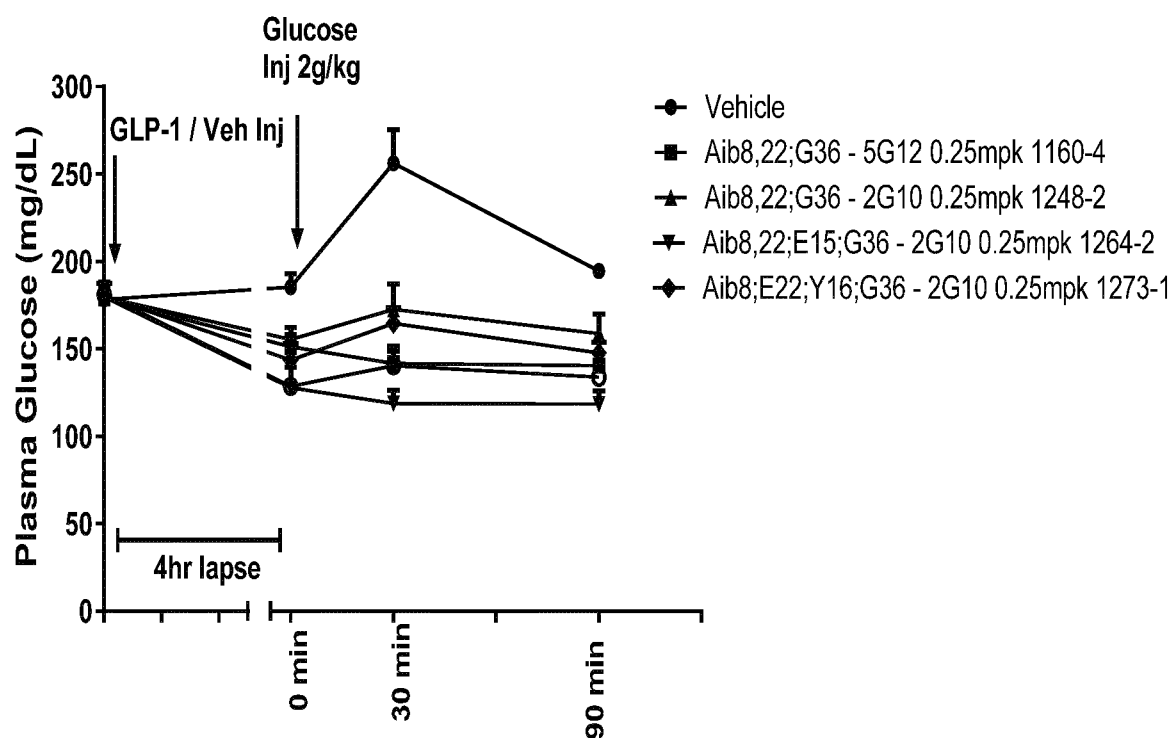
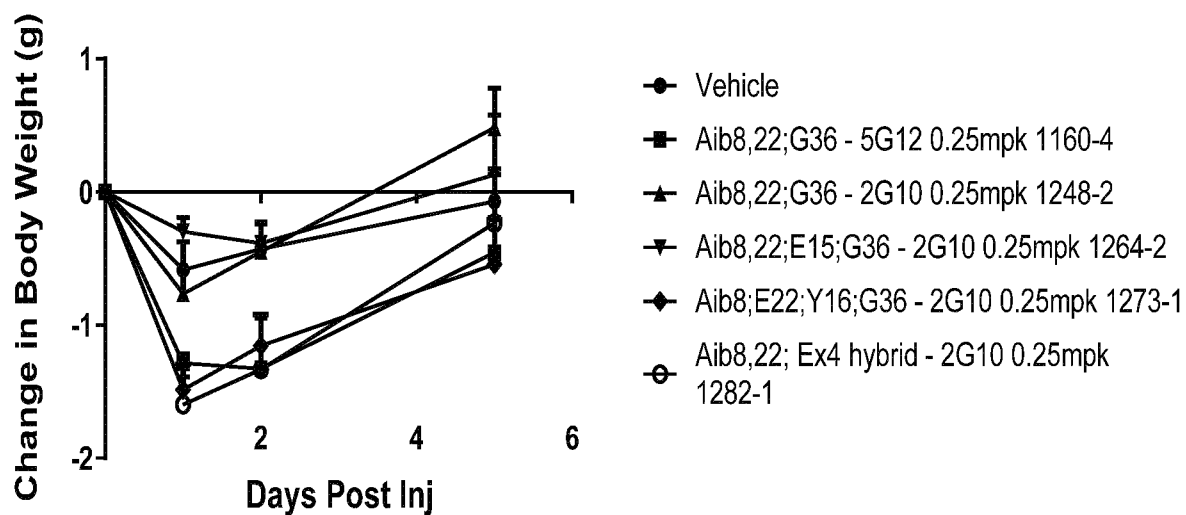


FIG. 5D



REPLACEMENT SHEET

21/40

FIG. 6A

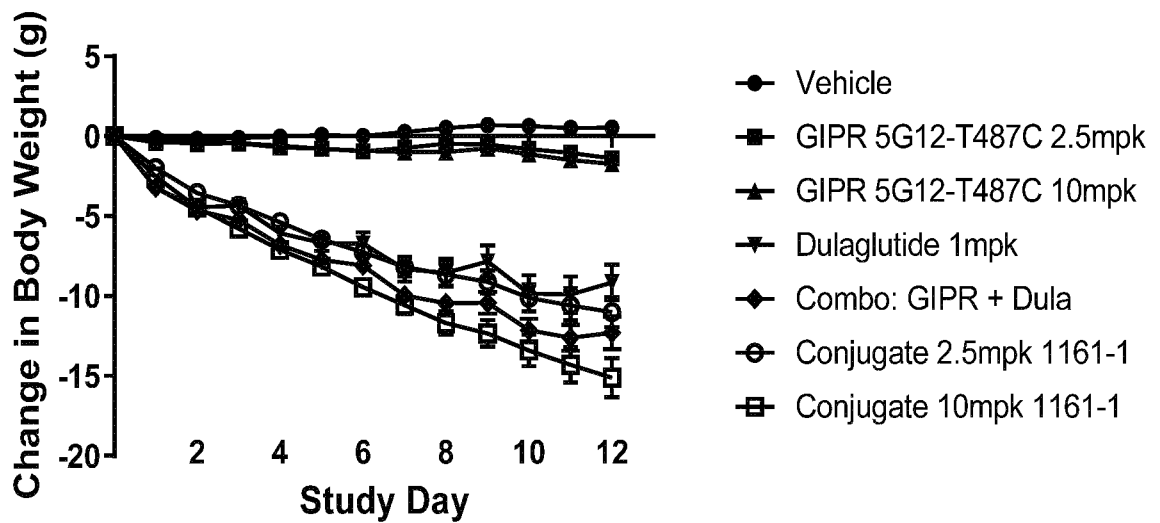
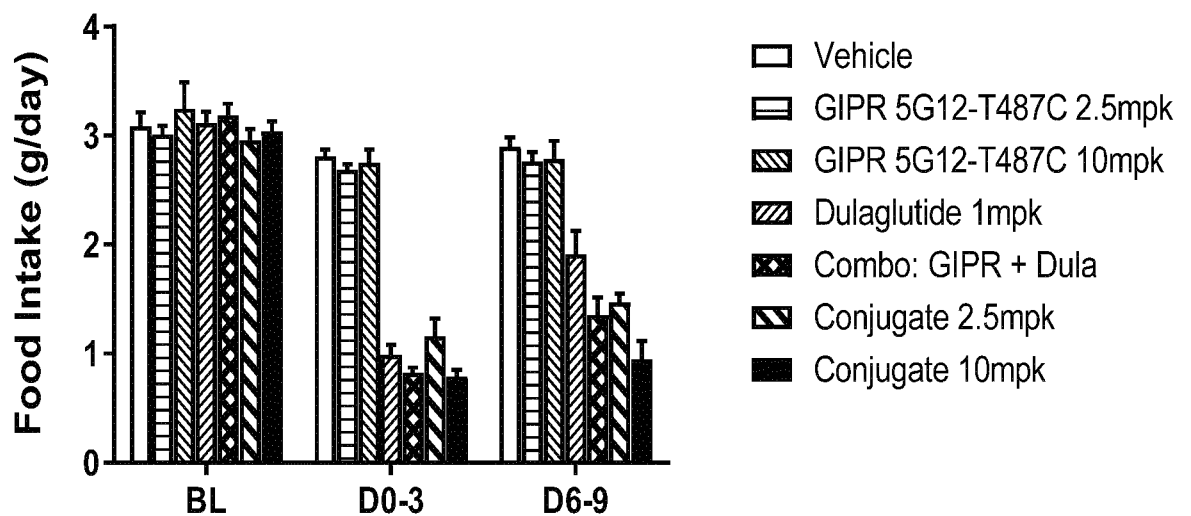


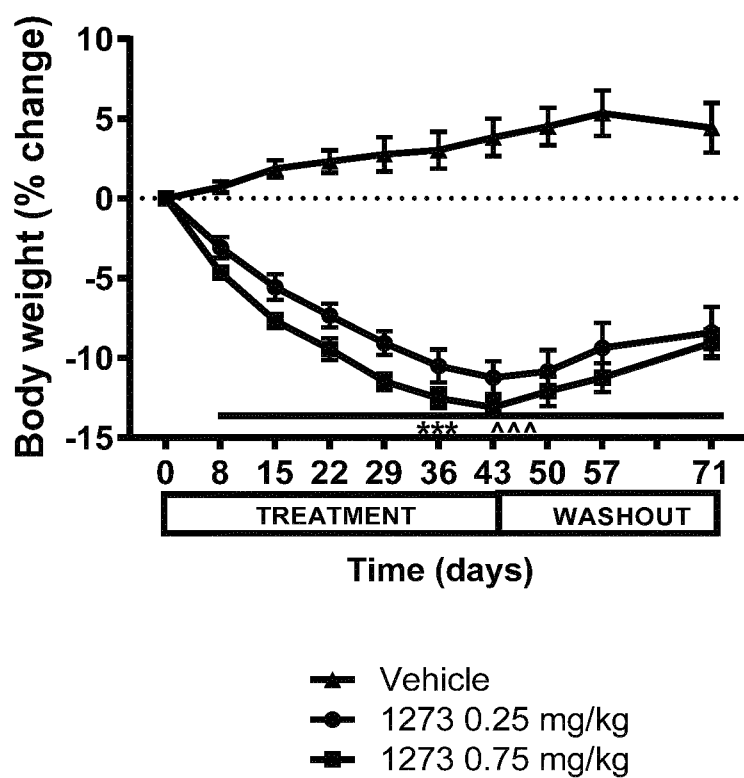
FIG. 6B



REPLACEMENT SHEET

22/40

FIG. 7

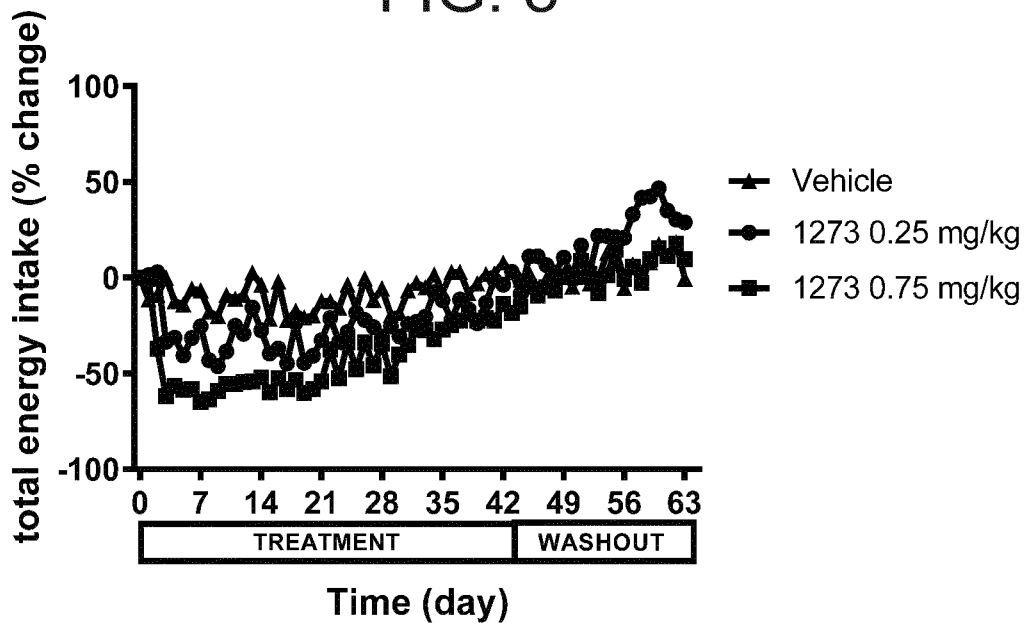


ANCOVA; *** $p < 0.001$ vs vehicle for 0.25 mg/kg; ^^^ $p < 0.001$ vs vehicle for 0.75 mg/kg
Data represented as group mean $\pm$ SEM; $n=8-9$ /group

REPLACEMENT SHEET

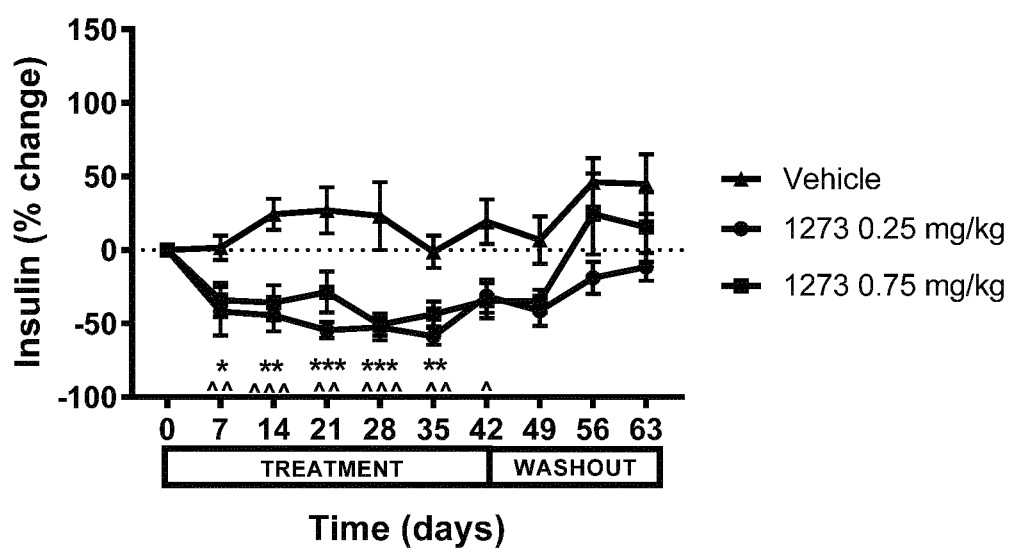
23/40

FIG. 8



Statistical analysis not performed on total energy intake; error bars not shown; data represented as group mean; n=8-9/group

FIG. 9

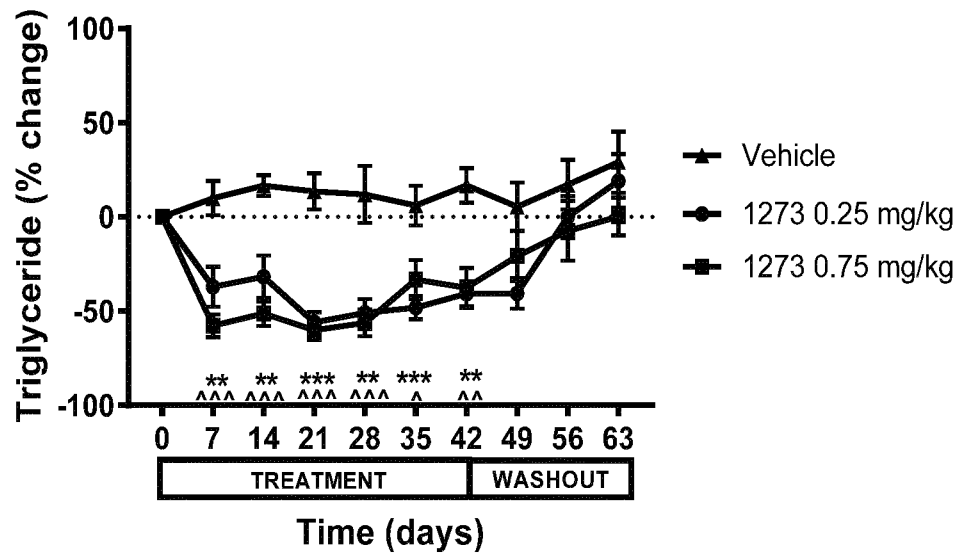


ANCOVA; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs vehicle for 0.25 mg/kg; ^ $p < 0.05$, ^^ $p < 0.01$, ^^ $p < 0.001$ vs vehicle for 0.75 mg/kg Data represented as group mean $\pm$ SEM; n=8-9/group

REPLACEMENT SHEET

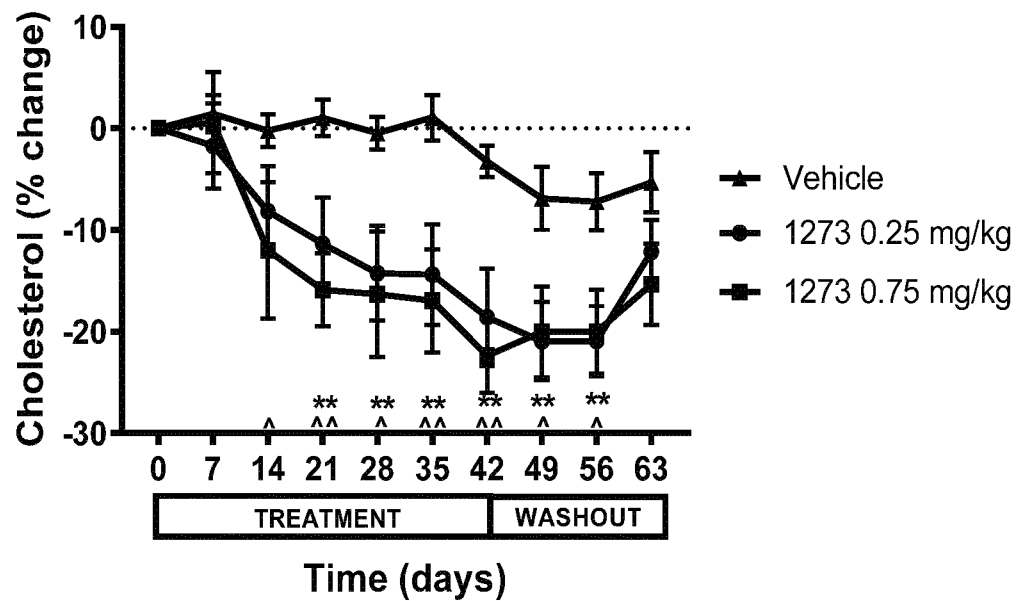
24/40

FIG. 10



ANCOVA; **p<0.01, ***p<0.001 vs vehicle for 0.25 mg/kg; ^p<0.05, ^^p<0.01, ^^p<0.001 vs vehicle or 0.75 mg/kg Data represented as group mean $\pm$ SEM; n=8-9/group

FIG. 11

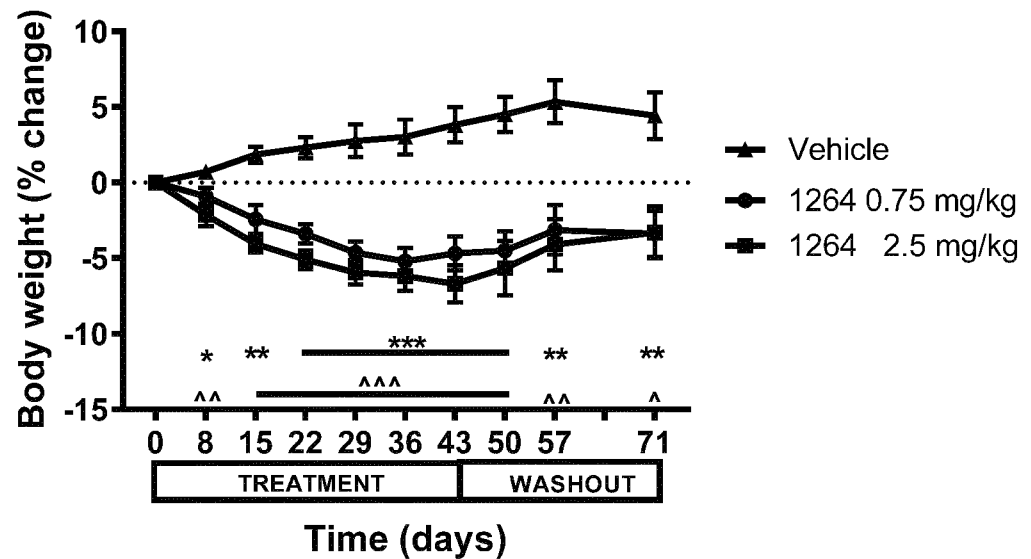


ANCOVA; **p<0.01 vs vehicle for 0.25 mg/kg; ^p<0.05, ^^p<0.01 vs vehicle for 0.75 mg/kg Data represented as group mean $\pm$ SEM; n=8-9/group

REPLACEMENT SHEET

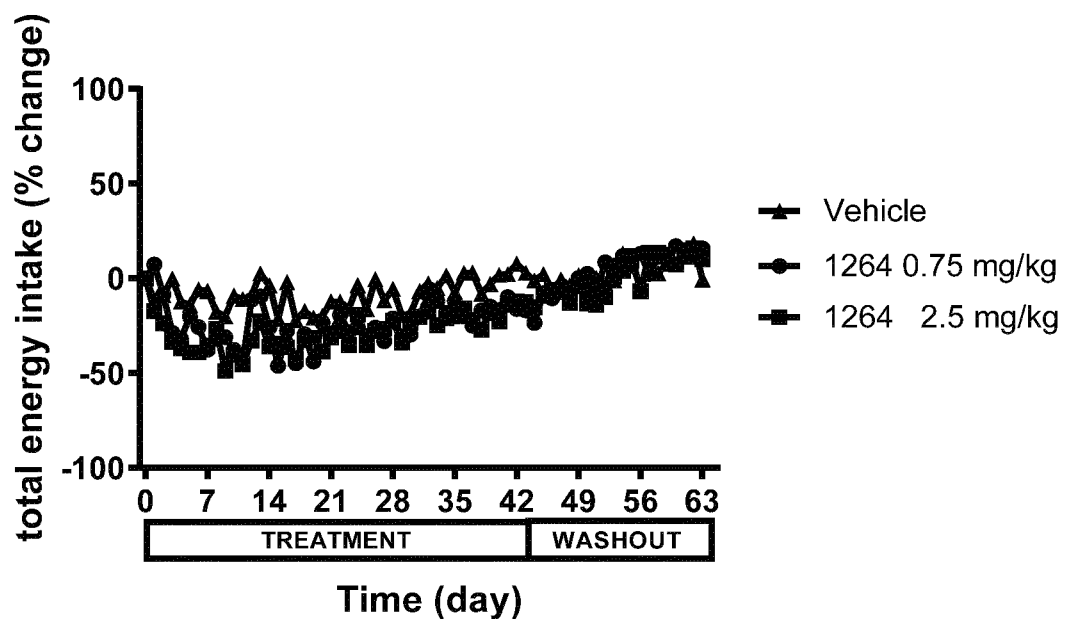
25/40

FIG. 12



ANCOVA; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs vehicle for 0.75 mg/kg; ^ $p < 0.05$, ^^ $p < 0.01$, ^^ $p < 0.001$ vs vehicle for 2.5 mg/kg Data represented as group mean $\pm$ SEM; $n = 9/\text{group}$

FIG. 13

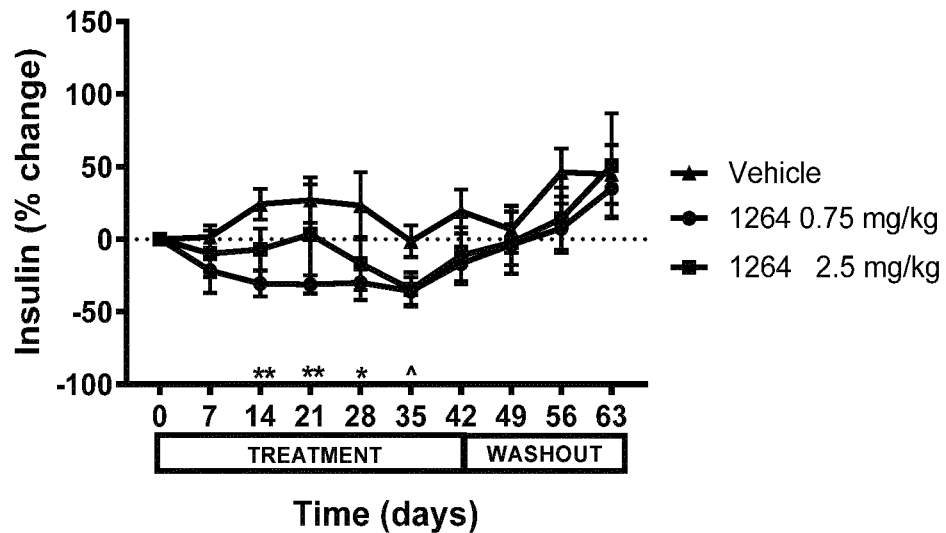


Statistical analysis not performed on total energy intake; error bars not shown; data represented as group mean; $n = 9/\text{group}$

REPLACEMENT SHEET

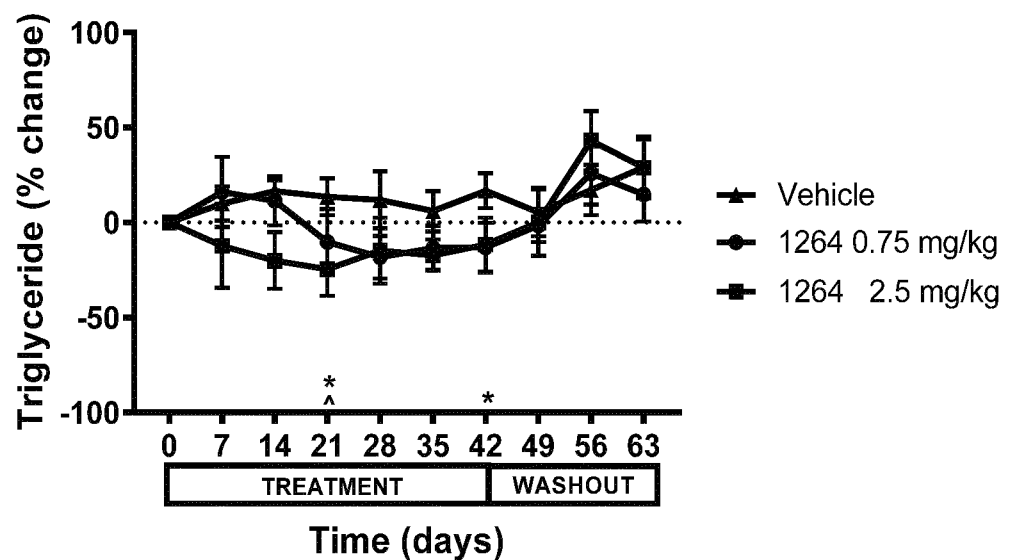
26/40

FIG. 14



ANCOVA; * $p < 0.05$, ** $p < 0.01$ vs vehicle for 0.75 mg/kg; ^ $p < 0.05$ vs vehicle for 2.5 mg/kg
 Data represented as group mean $\pm$ SEM; $n=9$ /group

FIG. 15

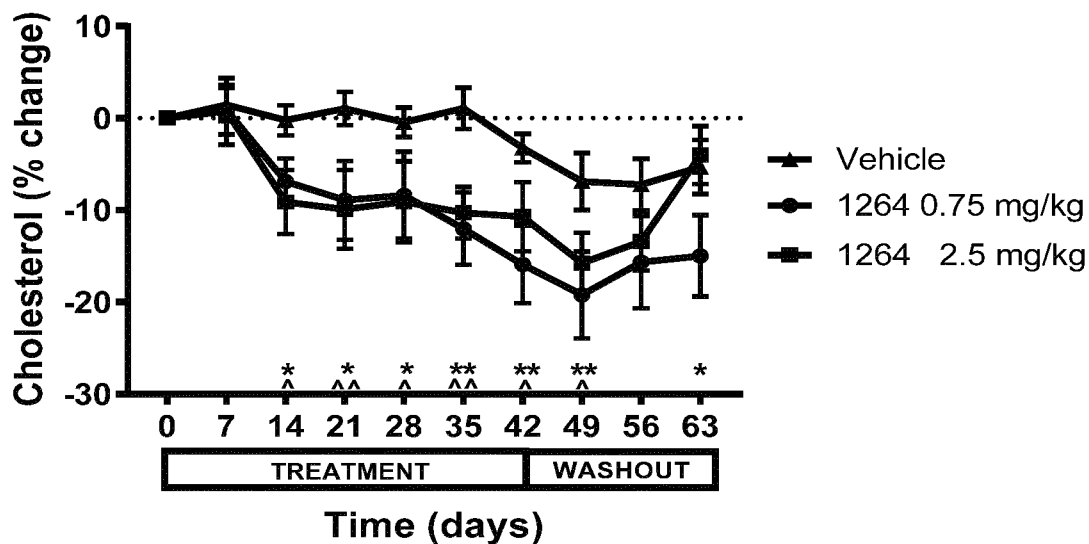


ANCOVA; * $p < 0.05$ vs vehicle for 0.75 mg/kg; ^ $p < 0.05$ vs vehicle for 2.5 mg/kg
 Data represented as group mean $\pm$ SEM; $n=9$ /group

REPLACEMENT SHEET

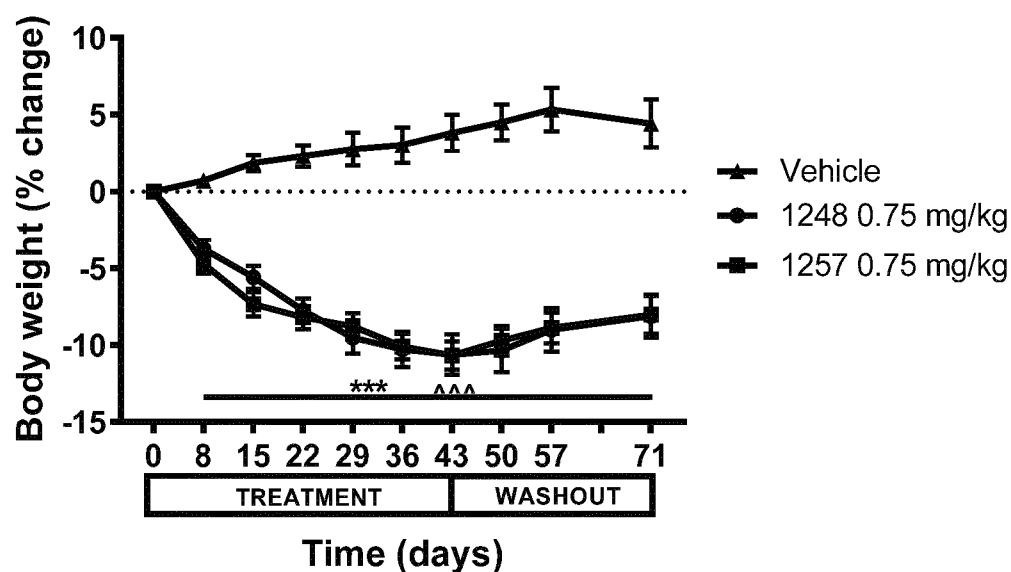
27/40

FIG. 16



ANCOVA; * $p < 0.05$, ** $p < 0.01$ vs vehicle for 0.75 mg/kg; $\wedge p < 0.05$, $\wedge\wedge p < 0.01$ vs vehicle for 2.5 mg/kg Data represented as group mean $\pm$ SEM; $n=9$ /group

FIG. 17

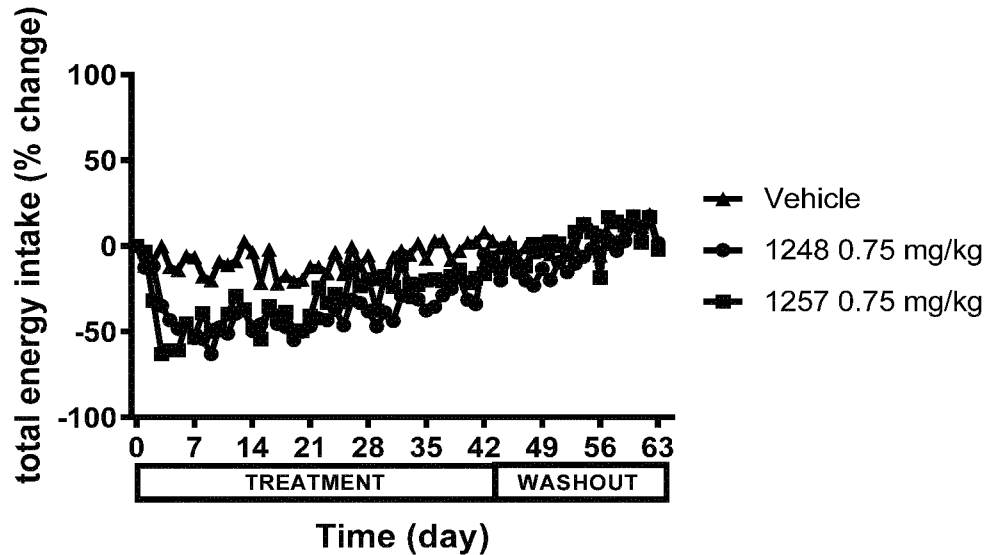


ANCOVA; *** $p < 0.001$ vs vehicle for 1248 0.75 mg/kg; $\wedge\wedge\wedge p < 0.001$ vs vehicle for 1257 0.75 mg/kg Data represented as group mean $\pm$ SEM; $n=7-10$ /group

REPLACEMENT SHEET

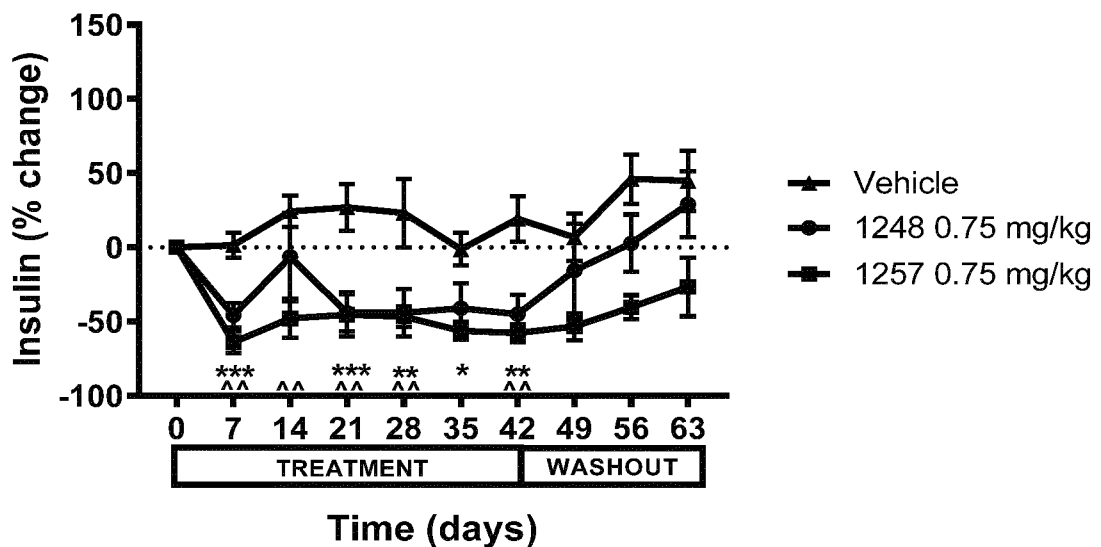
28/40

FIG. 18



ANCOVA; *** $p < 0.001$ vs vehicle for 1248 0.75 mg/kg; ^^ $p < 0.001$ vs vehicle for 1257 0.75 mg/kg Data represented as group mean $\pm$ SEM; $n = 7-10$ /group

FIG. 19

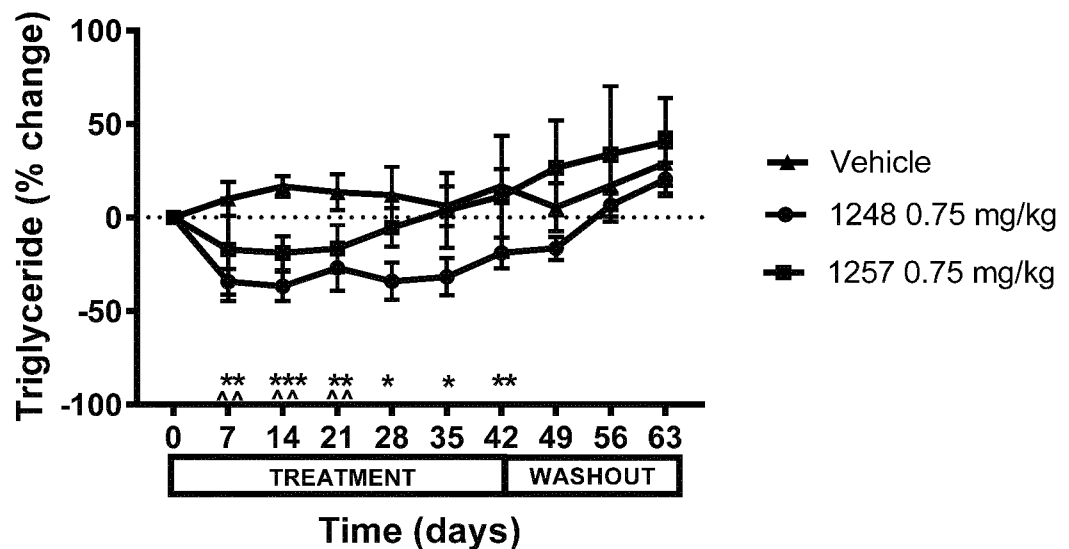


ANCOVA; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs vehicle for 1248 0.75 mg/kg;
^^ $p < 0.01$ vs vehicle for 1257 0.75 mg/kg
Data represented as group mean $\pm$ SEM; $n = 7-10$ /group

REPLACEMENT SHEET

29/40

FIG. 20

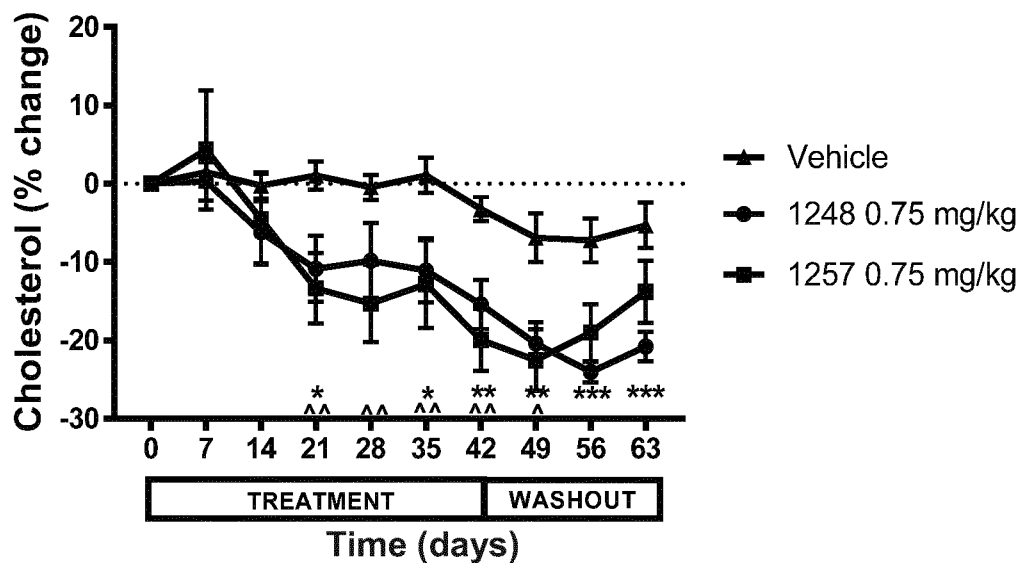


ANCOVA; *p<0.05, **p<0.01, ***p<0.001 vs vehicle for 1248 0.75 mg/kg;

^^p<0.01 vs vehicle for 1257 0.75 mg/kg

Data represented as group mean $\pm$ SEM; n=7-10/group

FIG. 21



ANCOVA; *p<0.05, **p<0.01, ***p<0.001 vs vehicle for 1248 0.75 mg/kg; ^p<0.05,

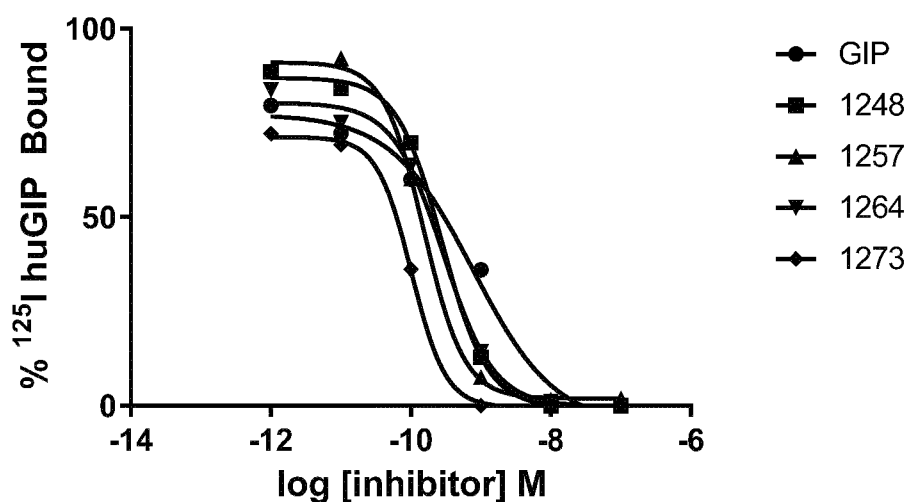
^^p<0.01 vs vehicle for 1257 0.75 mg/kg

Data represented as group mean $\pm$ SEM; n=7-10/group

REPLACEMENT SHEET

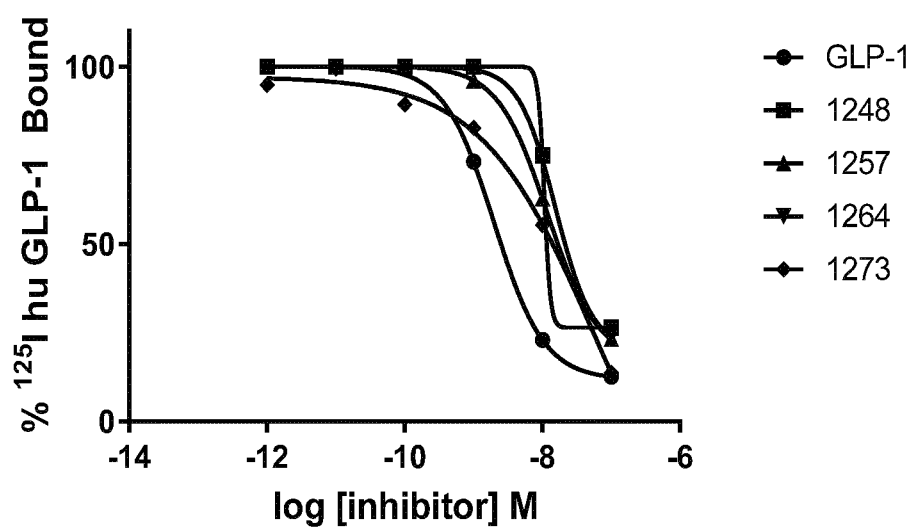
30/40

FIG. 22A

¹²⁵I huGIP Radioligand Binding Assay

	GIP	1248	1257	1264	1273
IC50	7.788e-010	2.806e-010	1.539e-010	2.928e-010	1.021e-010

FIG. 22B

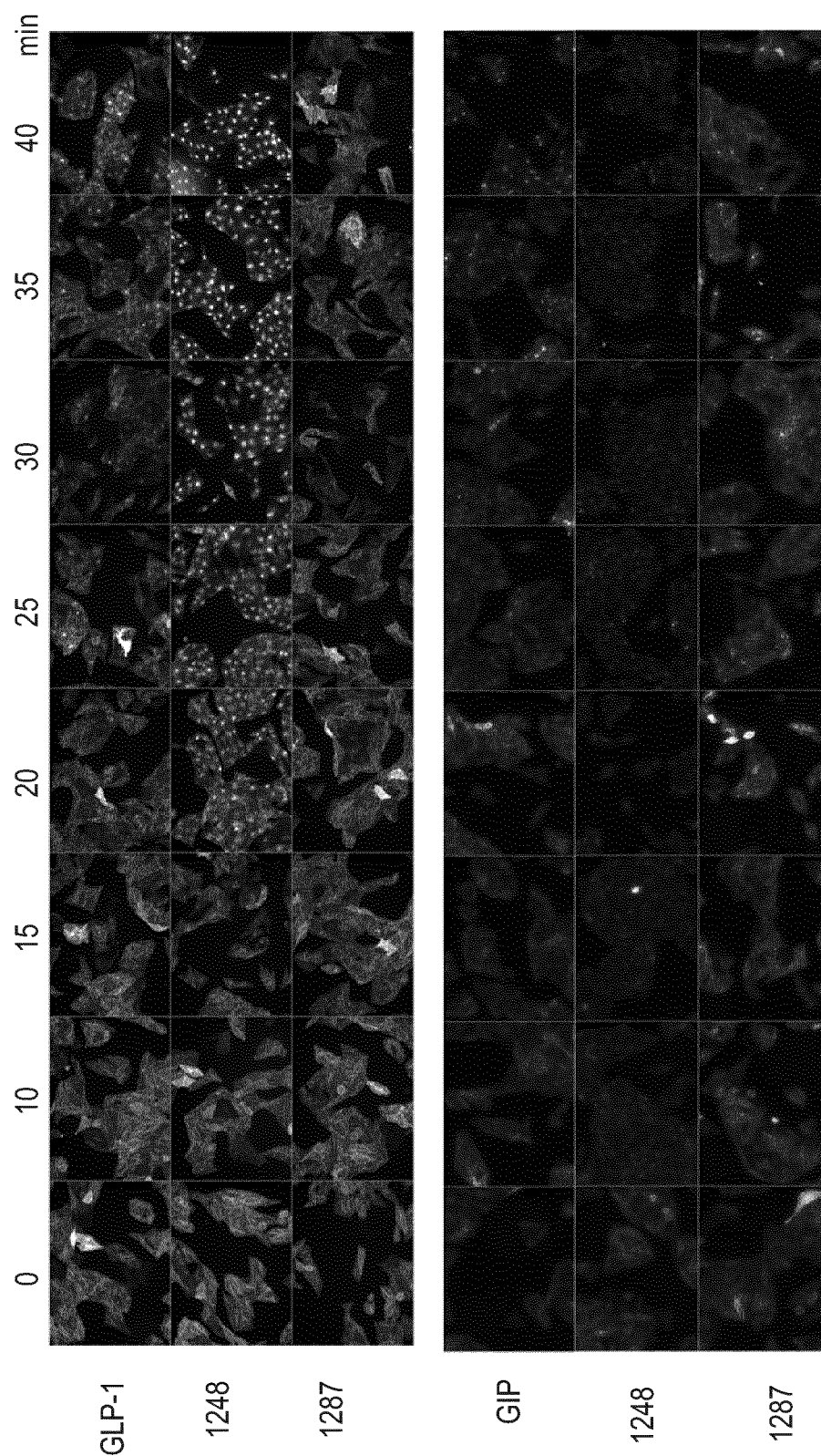
¹²⁵I huGLP-1 Radioligand Binding Assay

	GLP-1	1248	1257	1264	1273
IC50	1.995e-009	1.069e-008	1.174e-008	1.548e-008	5.627e-008

REPLACEMENT SHEET

31/40

FIG. 23



REPLACEMENT SHEET

32/40

FIG. 24A

GLP1R Internalization in CHOK1 GIPR/GLP-1R M1 cells

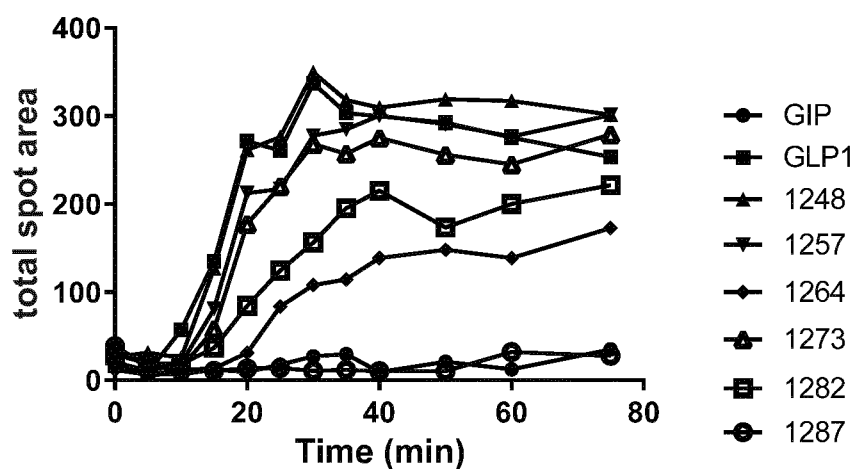
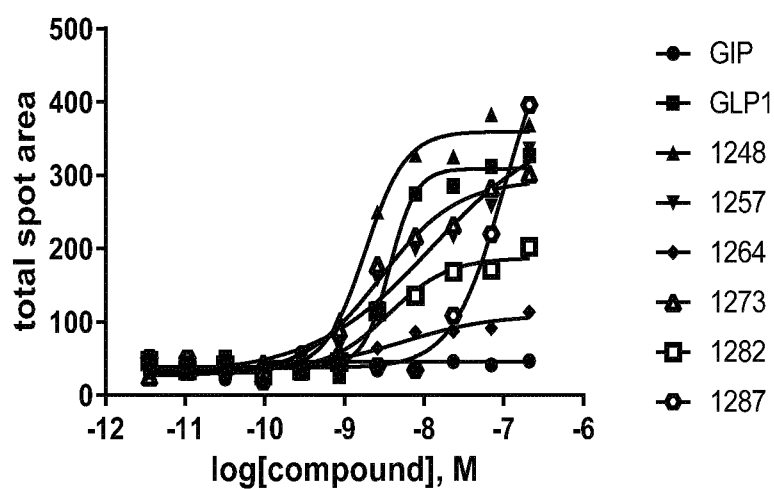


FIG. 24B

GLP-1R Internalization in CHOK1 GIPR/GLP-1R M1 cells



	GIP	GLP1	1248	1257	1264	1273	1282	1287
EC50	~9.480e-011	3.689e-009	1.834e-009	1.235e-008	5.348e-009	2.830e-009	3.606e-009	1.033e-007

REPLACEMENT SHEET

33/40

FIG. 25A

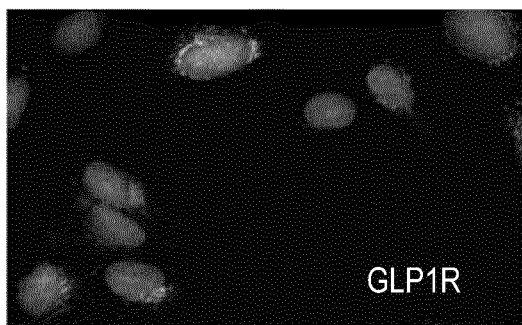


FIG. 25B

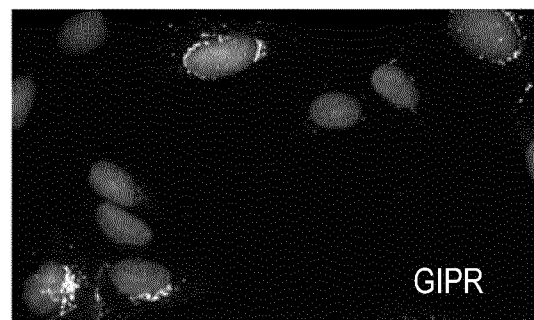


FIG. 25C

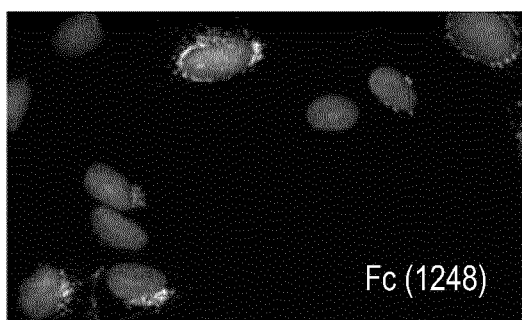
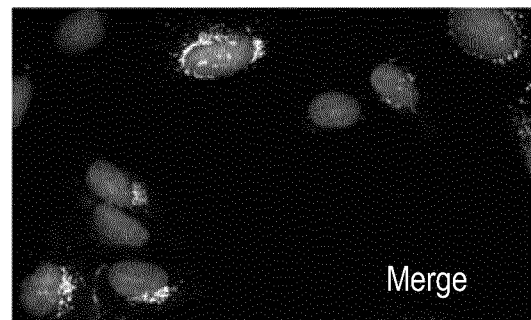


FIG. 25D



REPLACEMENT SHEET

34/40

FIG. 26A

Effects of inhibition of receptor internalization on
1248 induced cAMP activity

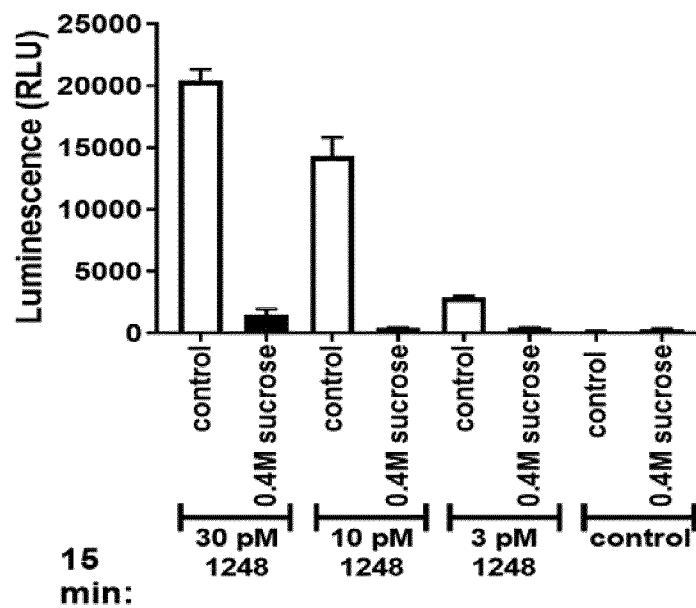
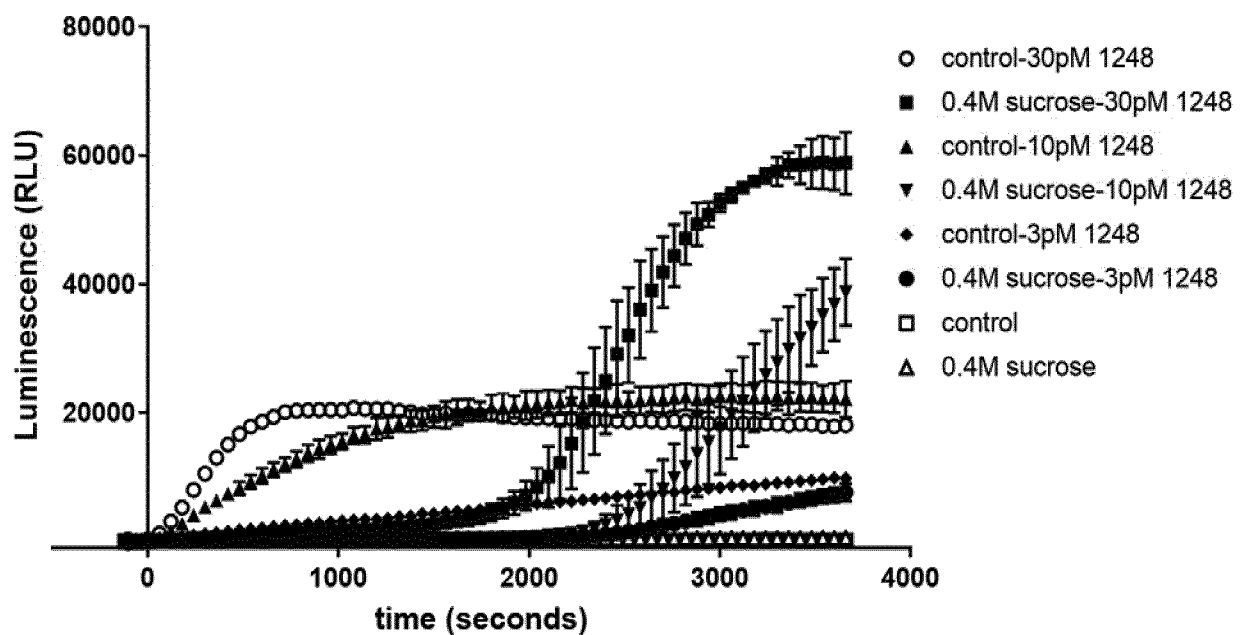


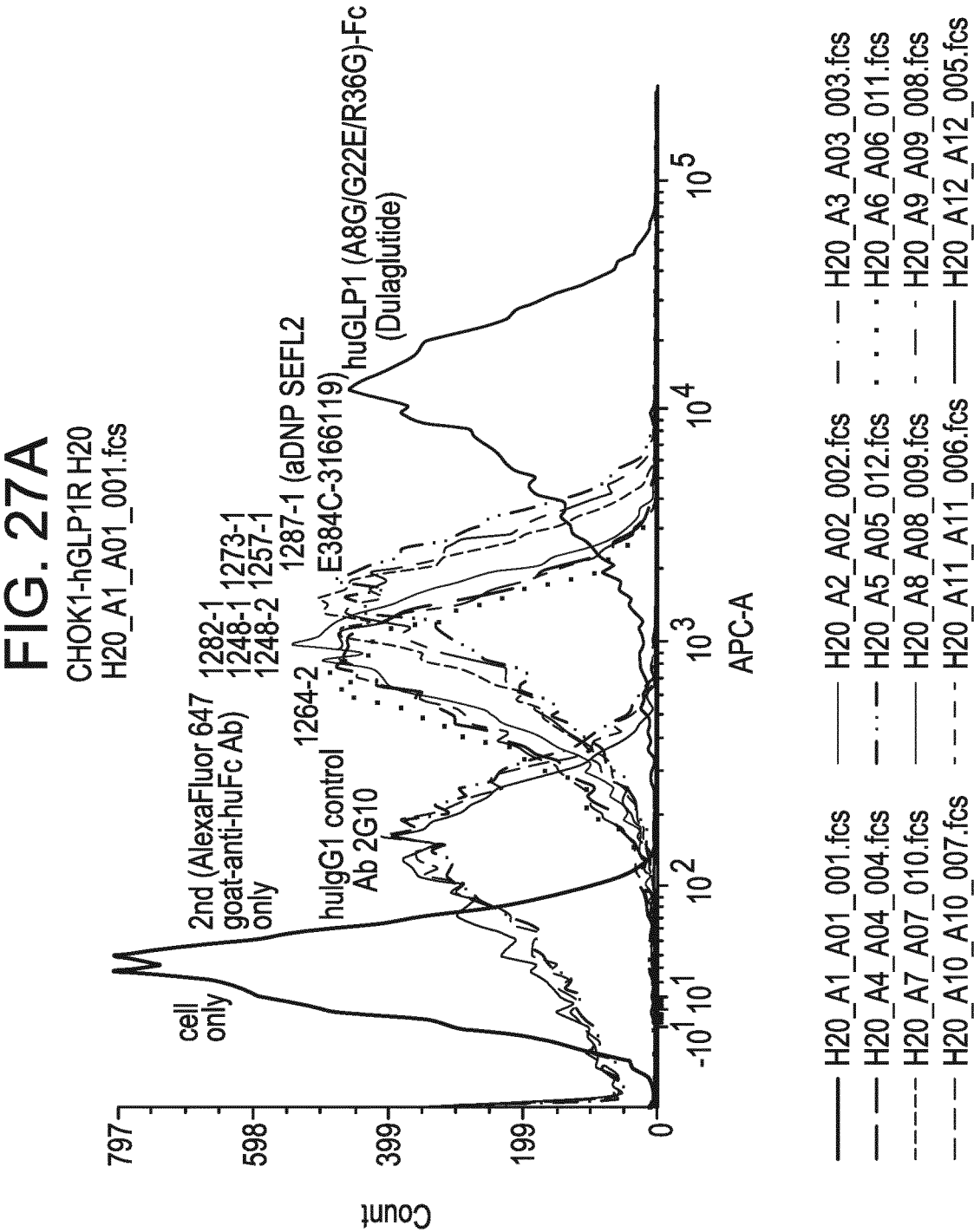
FIG. 26B

GloSensor cAMP assay
1248



REPLACEMENT SHEET

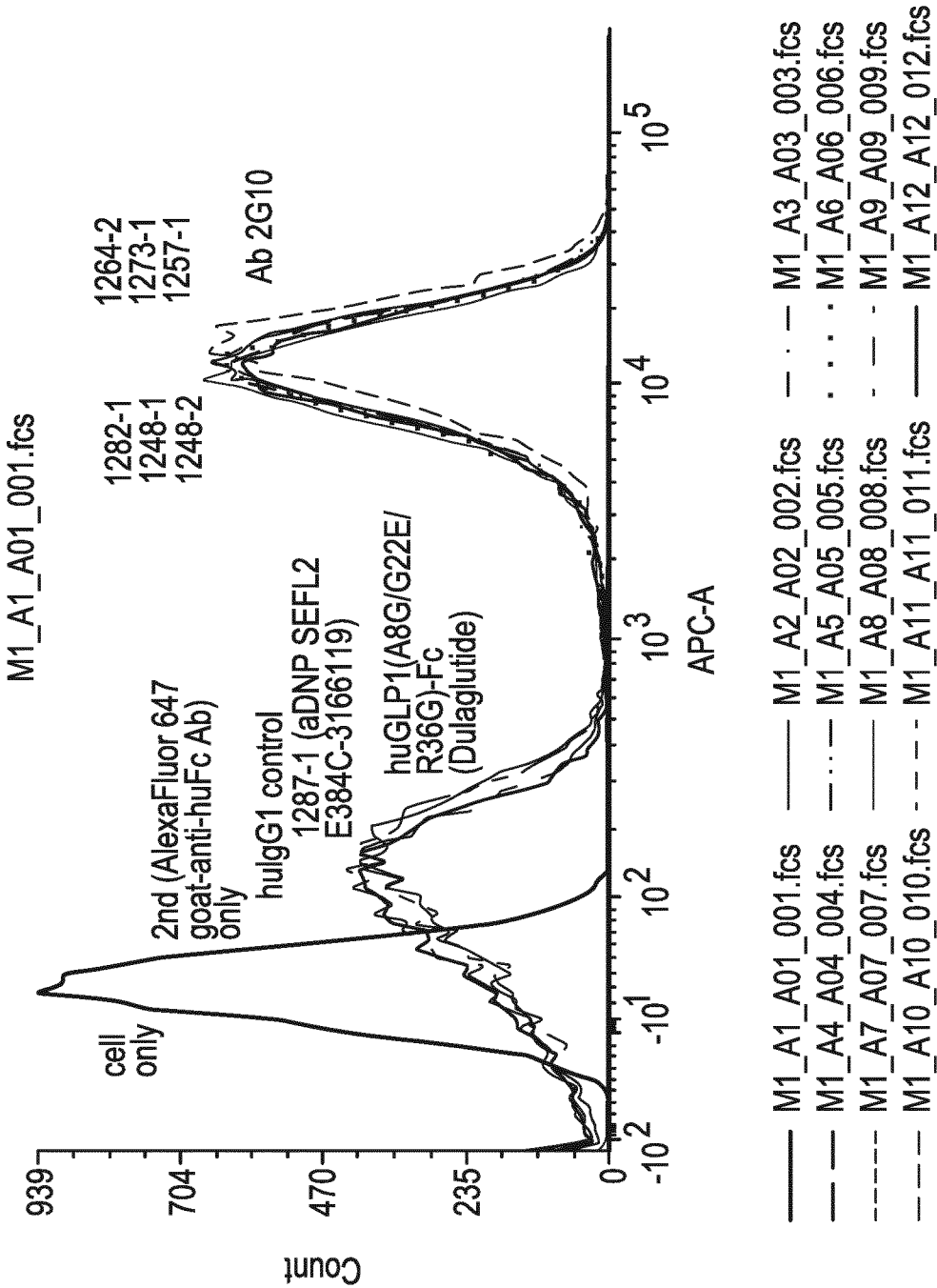
35/40



REPLACEMENT SHEET

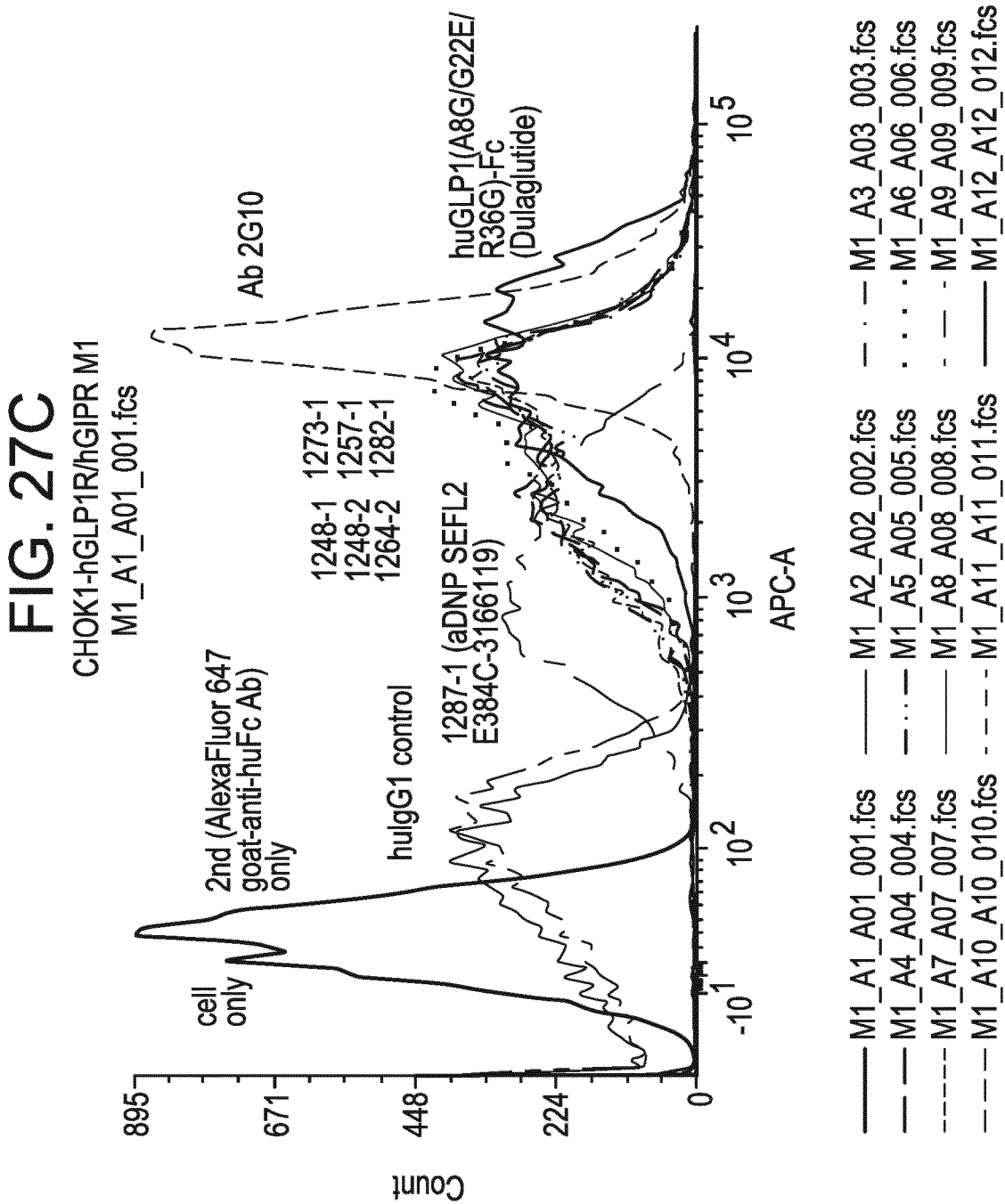
36/40

FIG. 27B
293T-GIPR clone 10
M1_A1_A01_001.fcs



REPLACEMENT SHEET

37/40

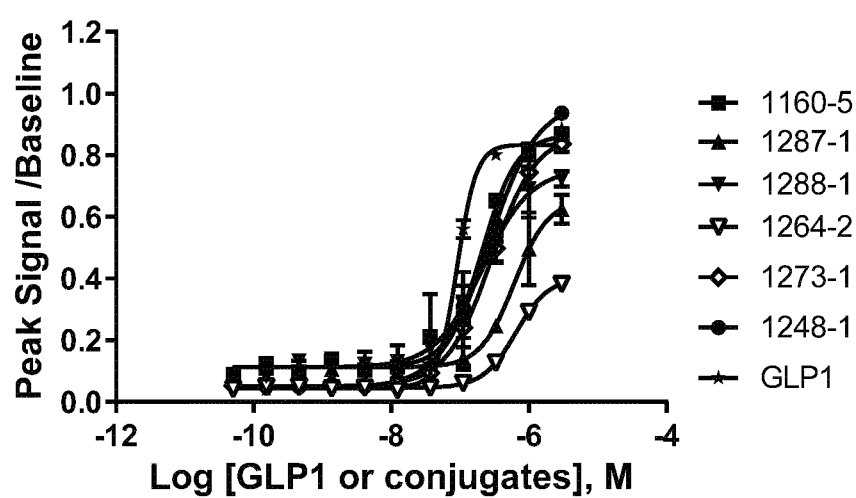


REPLACEMENT SHEET

38/40

FIG. 28

Calcium Flux assay in ChoK1 GLP1R/GIPR M1 cells

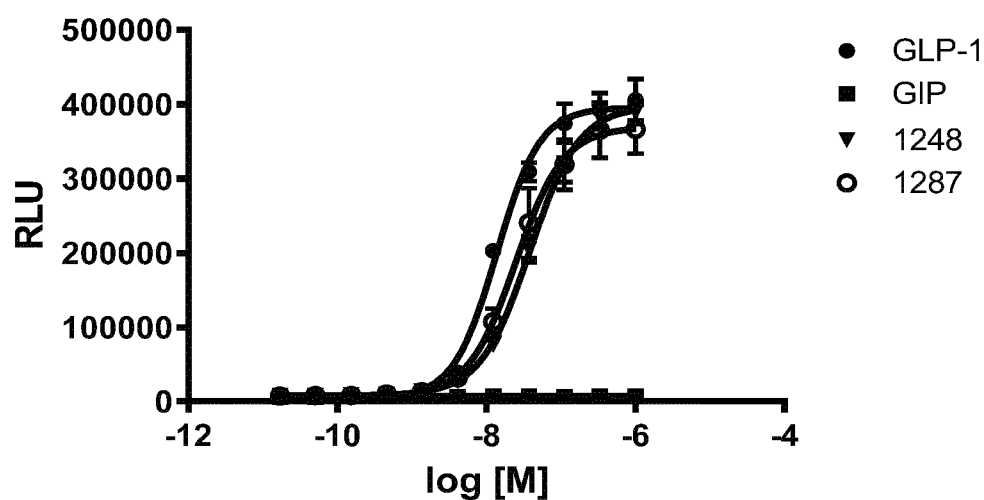


	1160-5	1287-1	1288-1	1264-2	1273-1	1248-1	GLP1
EC50	2.098e-007	6.152e-007	2.141e-007	6.485e-007	2.862e-007	2.594e-007	9.123e-008

REPLACEMENT SHEET

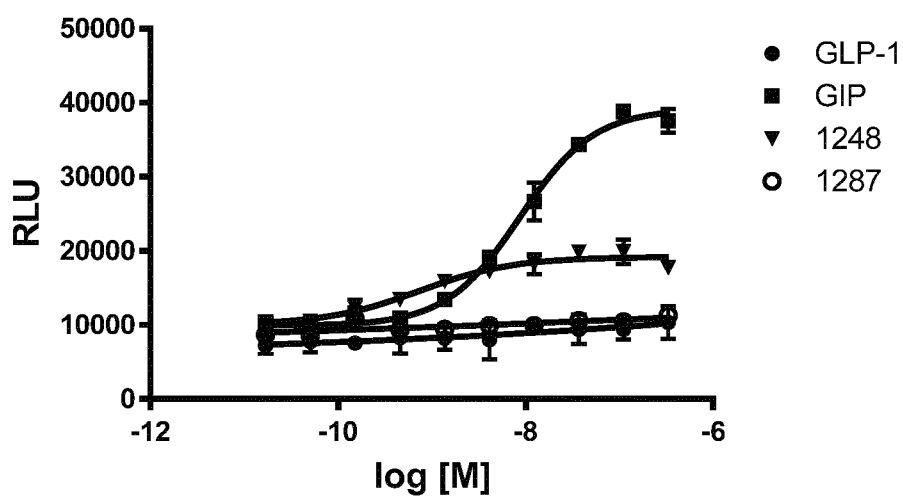
39/40

FIG. 29A

GLP-1R PathHunter/GIPR β -arrestin assay

	GIP	GLP-1	1248	1287
EC50	1.974e-010	1.379e-008	3.83e-008	2.493e-008

FIG. 29B

GIPR PathHunter/GLP-1R β -arrestin assay

	GLP-1	GIP	1248	1287
EC50	1.689e+017	8.702e-009	7.363e-010	~4.234e-006

REPLACEMENT SHEET

40/40

FIG. 30

Glucose-stimulated insulin secretion assay:
low and high glucose conditions in
human pancreatic microislets

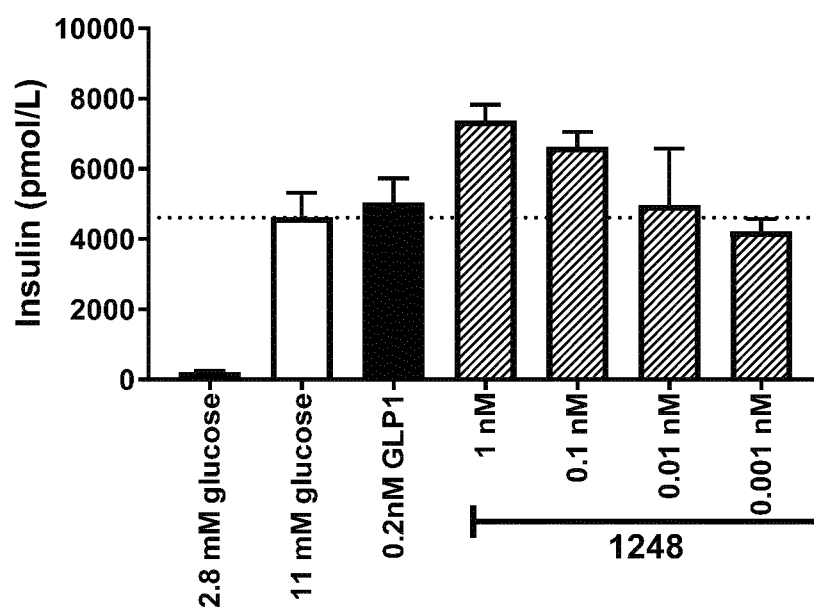
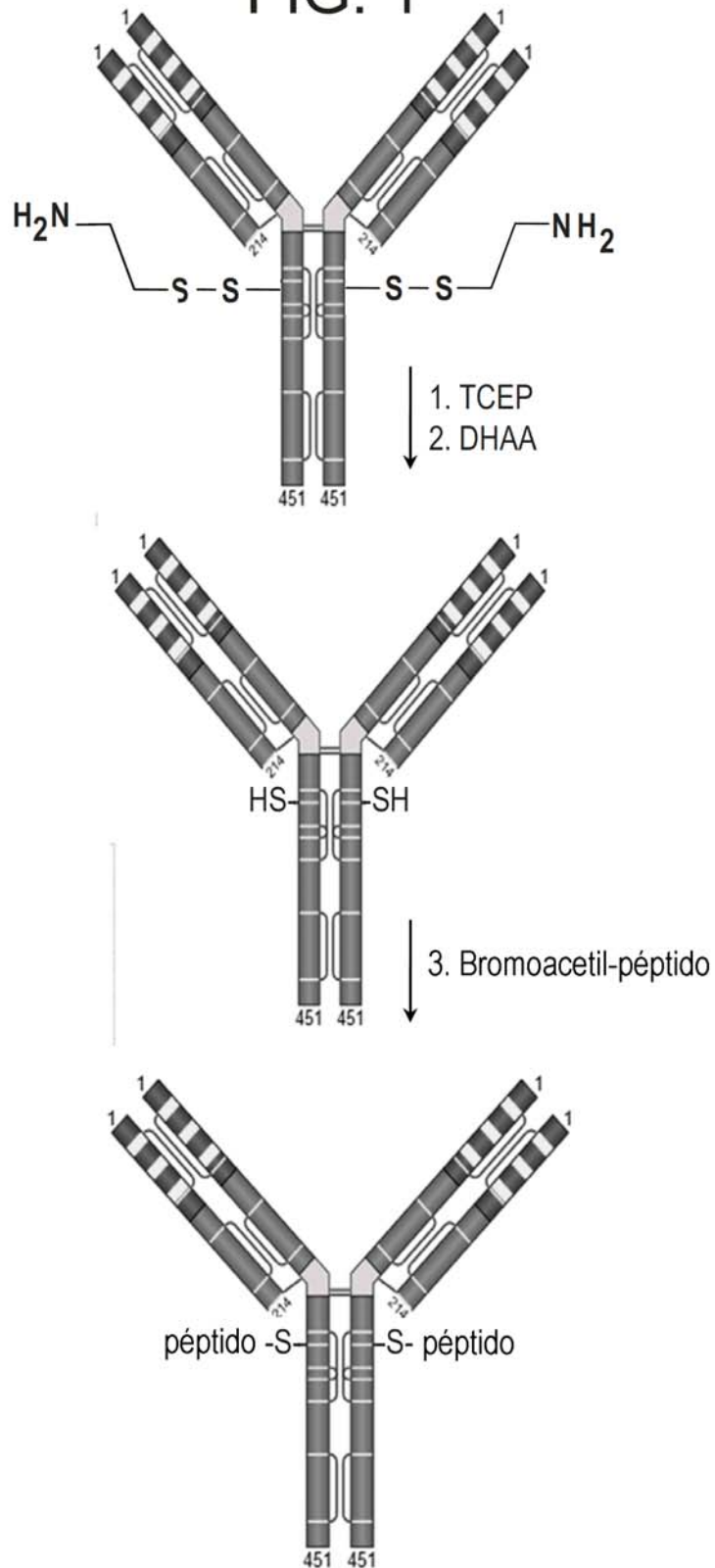


FIG. 1



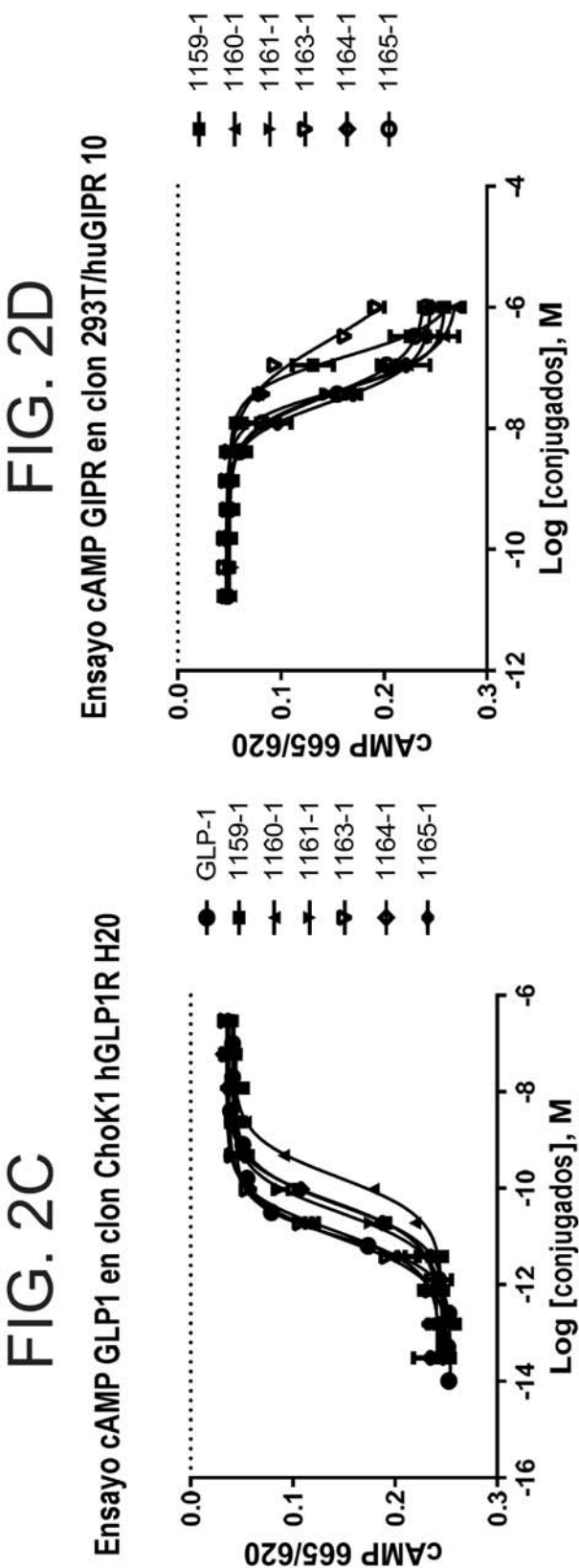
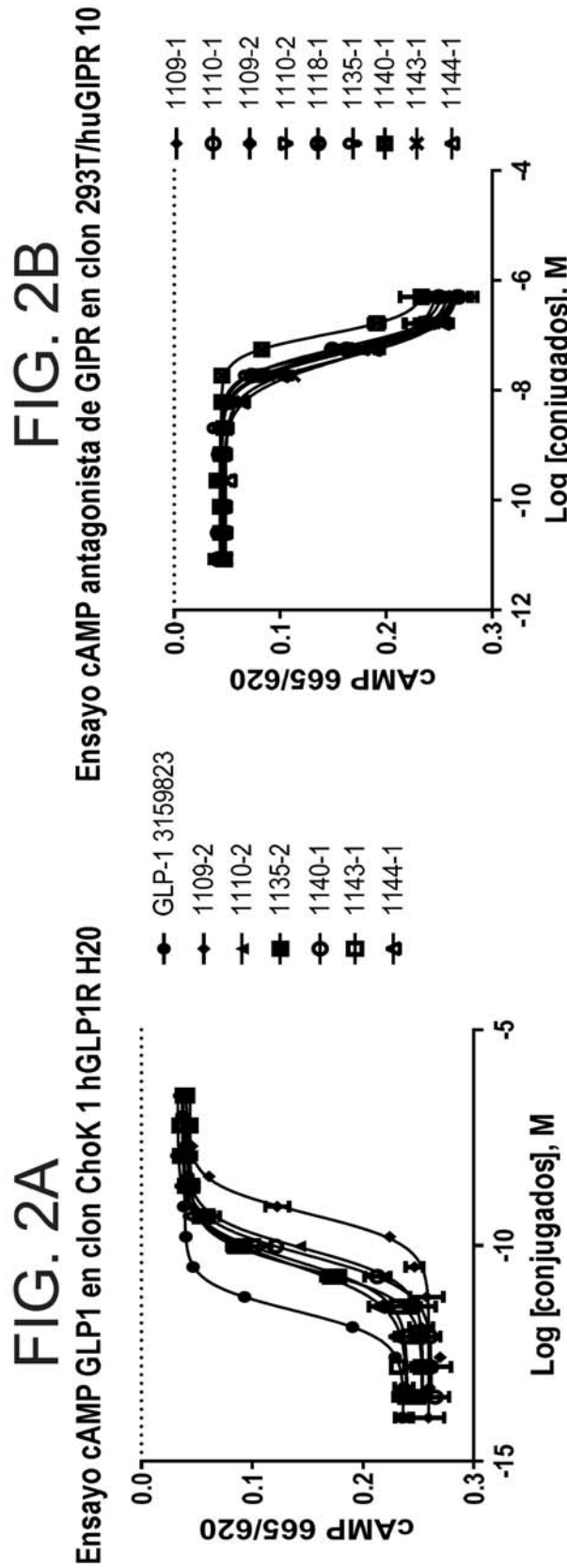


FIG. 2E

Ensayo cAMP (modo agonista de GLP-1) en CHOK1 hGLP1R H20

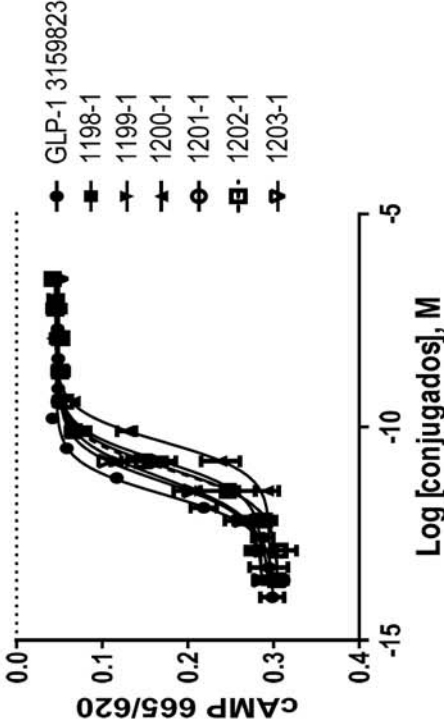


FIG. 2F

Ensayo cAMP (modo antagonista de GIPR) en 293T/hGIPR #10

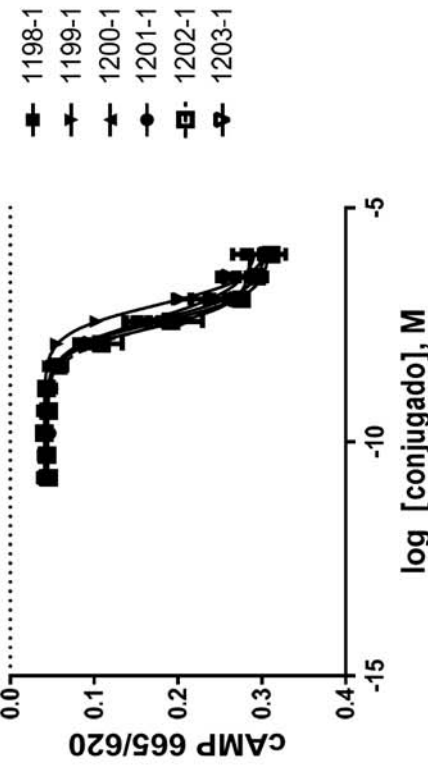


FIG. 2G

Ensayo cAMP (modo agonista de GLP-1) en CHOK1 hGLP1R H20

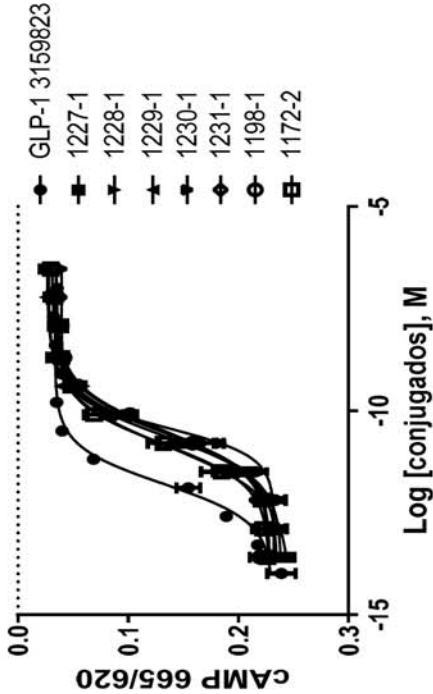


FIG. 2H

Ensayo cAMP (modo antagonista de GIPR) en 293T/hGIPR #10

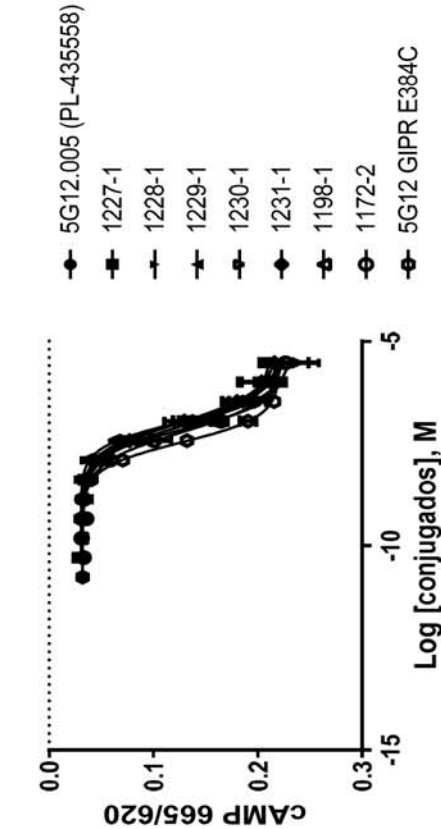


FIG. 2I

Ensayo cAMP (modo agonista de GLP-1) en CHOK1 hGLP1R H20

Ensayo cAMP (modo antagonista de GIPR) en 293T/hGIPR #10

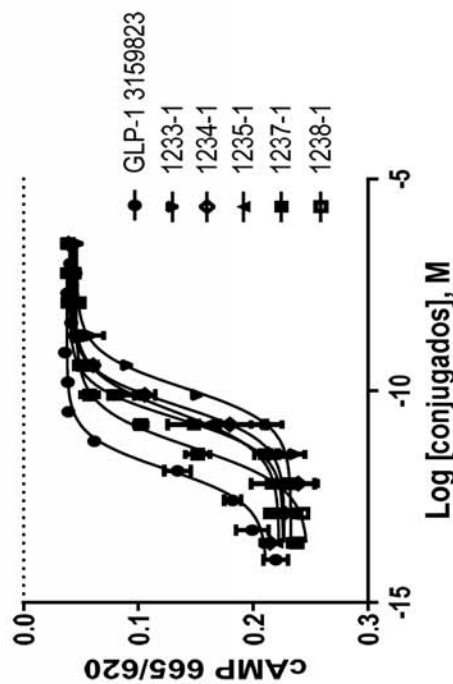


FIG. 2J

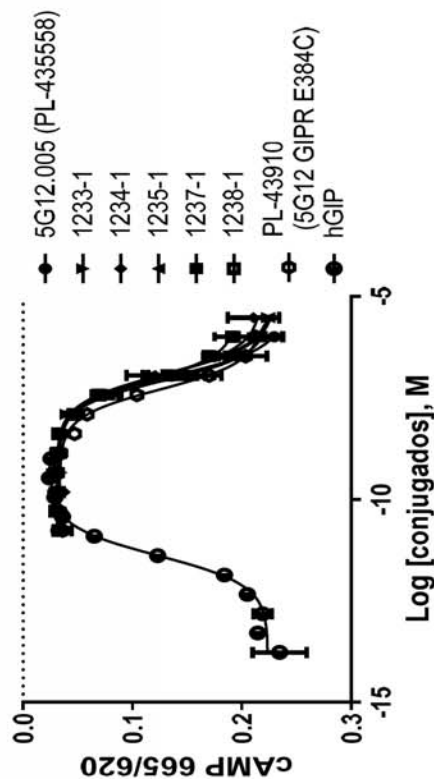


FIG. 2K

Ensayo cAMP (modo agonista de GLP-1) en CHOK1 hGLP1R H20

Ensayo cAMP (modo antagonista de GIPR) en 293T/hGIPR #10

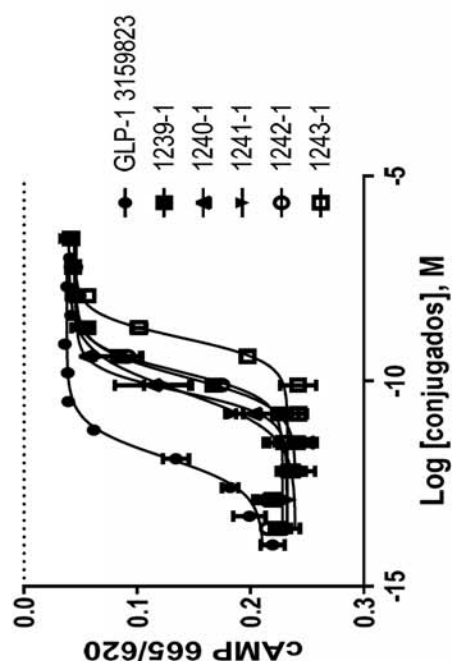


FIG. 2L

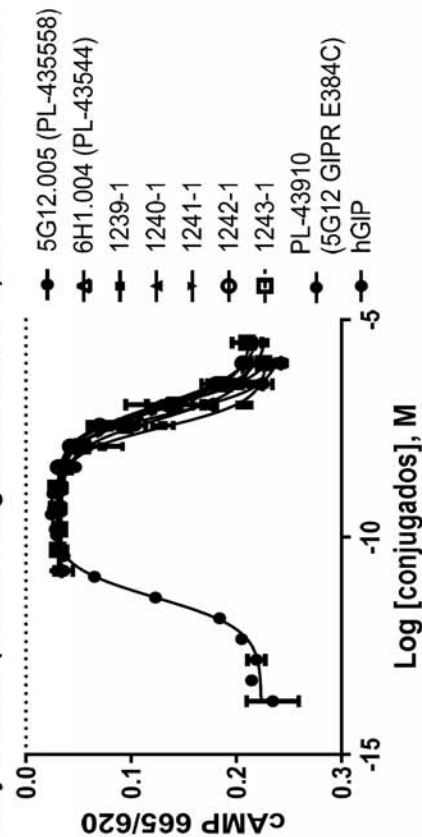
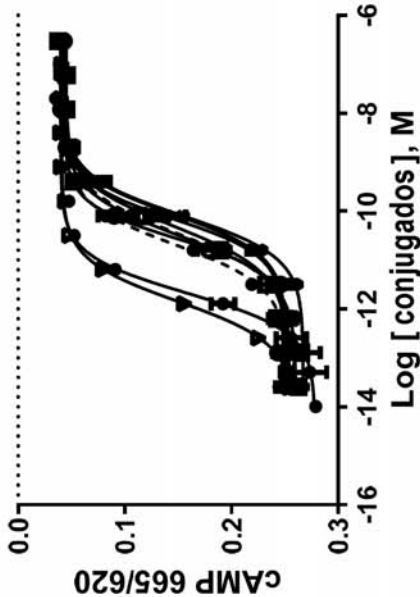


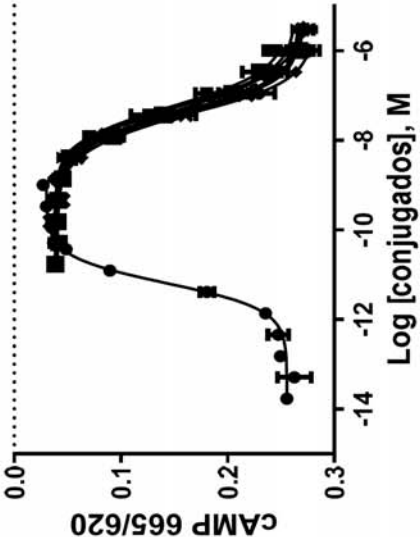
FIG. 2M

Ensayo cAMP (modo agonista de GLP-1) en CHOK1 hGLP1R H20: Ensayo cAMP (modo antagonista de GIPR) en 293T/hGIPR #10
Conjugados químicos en 5G12



- GLP-1 3159823
- Exendin-4
- 1160-4
- 1172-1
- 1227-3
- 1231-2
- 1234-1
- 1238-1
- 1250-2
- 1252-1

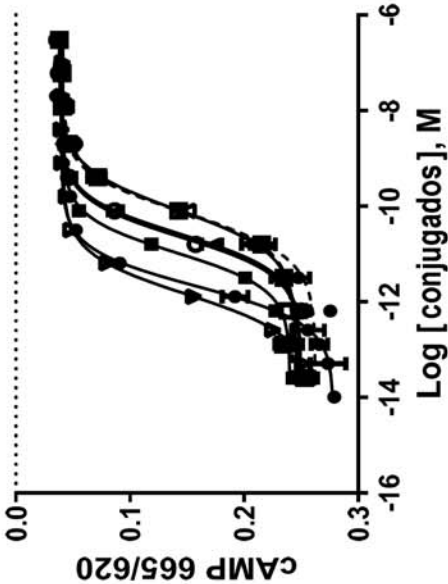
FIG. 2N



- hGIP
- 5G12.005 (PL-43558)
- 1160-4
- 1172-1
- 1227-3
- 1231-2
- 1234-1
- 1238-1
- 1250-2
- 1252-1

FIG. 20

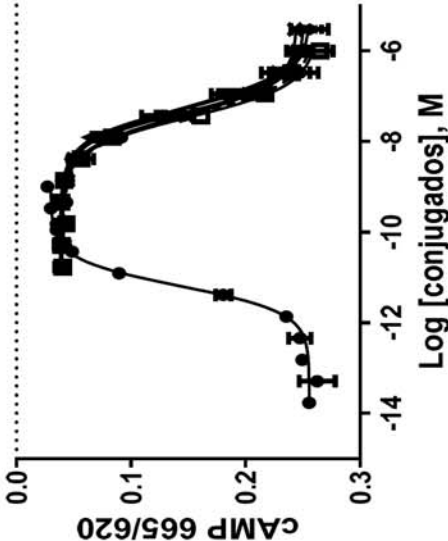
Ensayo cAMP (modo agonista de GLP-1) en CHOK1 hGLP1R H20:
Conjugados químicos en 5G12



- GLP-1 3159823
- Exendin-4
- 1253-2
- 1254-2
- ▲ 1269-1
- 1270-1
- 1283-1
- ▲ 1284-1

FIG. 2P

Ensayo cAMP (modo antagonista de GIPR) en 293T/hGIPR #10
Conjugados químicos en 5G12



- hGIP
- 5G12.005 (PL-43558)
- 1253-2
- 1254-2
- 1269-1
- 1270-1
- 1283-1
- 1284-1

FIG. 2Q

Ensayo cAMP (modo agonista de GLP-1) en CHOK1
hGLP1R H20: Conjugados químicos en 2G10

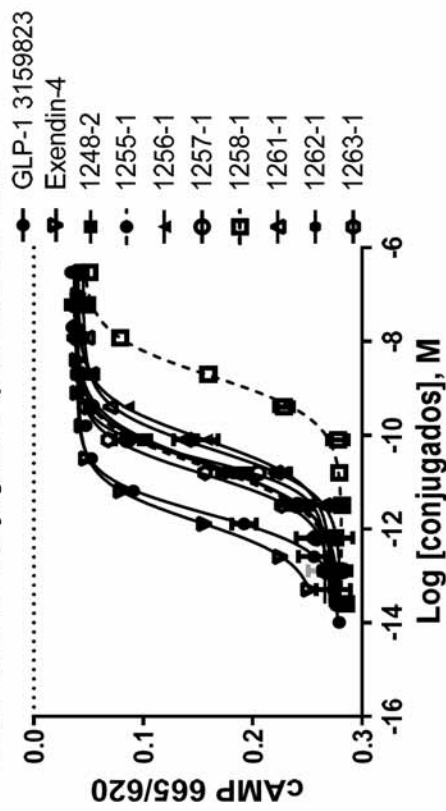


FIG. 2R

Ensayo cAMP (modo antagonista de GIPR) en
293T/hGIPR #10 Conjugados químicos en 2G10

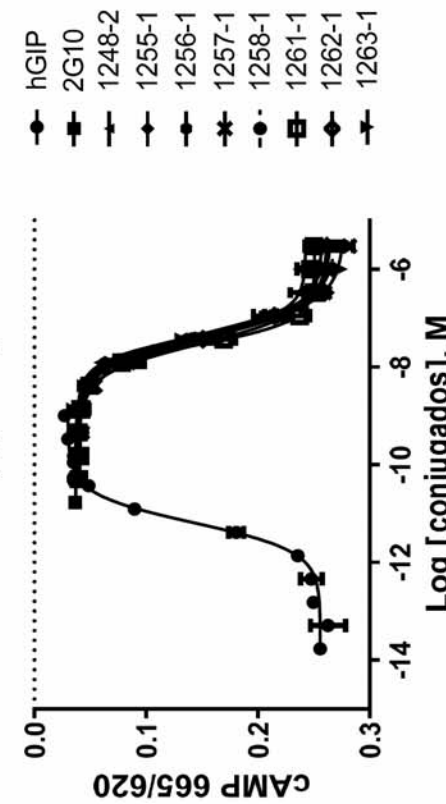


FIG. 2S

Ensayo cAMP (modo agonista de GLP-1) en CHOK1
hGLP1R H20: Conjugados químicos en 2G10

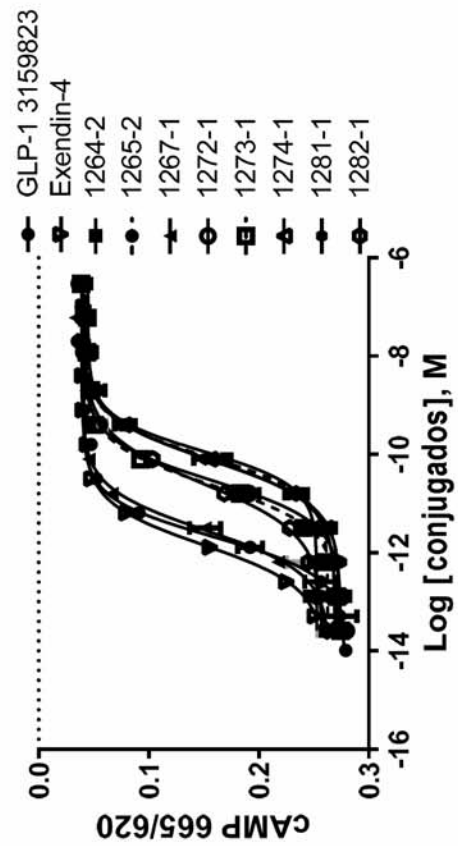


FIG. 2T

Ensayo cAMP (modo antagonista de GIPR) en
293T/hGIPR #10 Conjugados químicos en 2G10

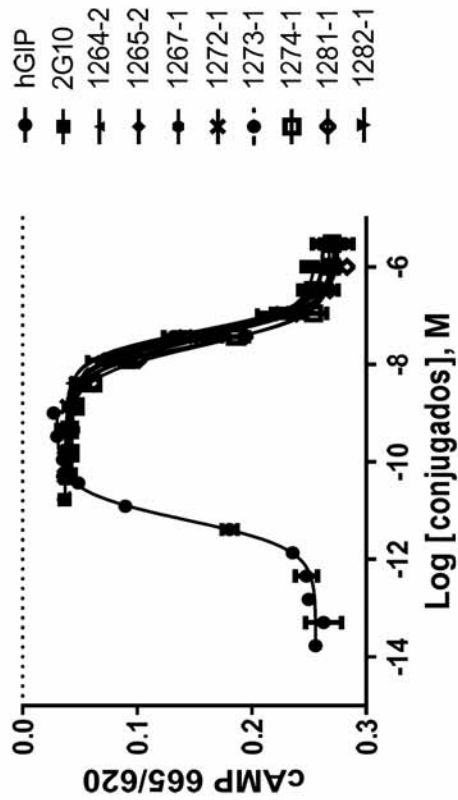
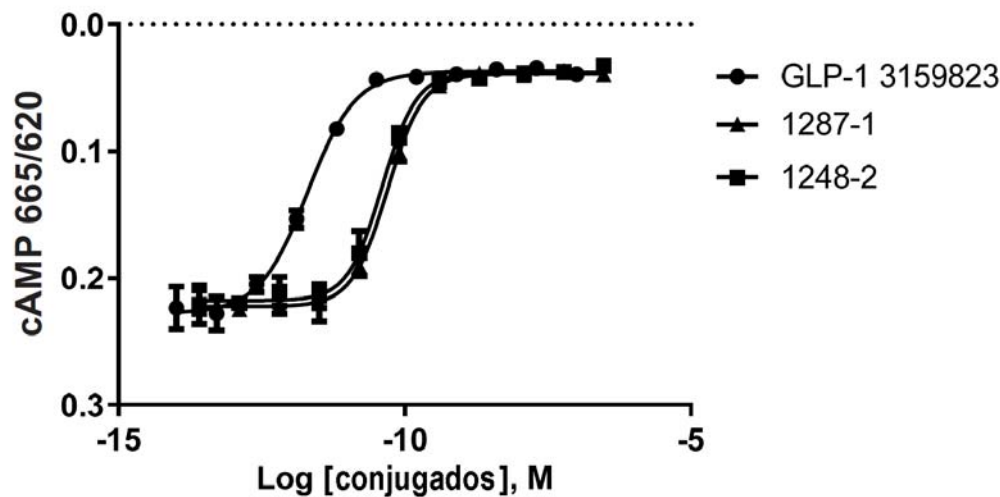


FIG. 3A

Reg #	Descripción	Información sobre el péptido	CHOK1 hGLP-1R	CHOK1 hGLP-1R/GIPR
1148	3166119-E384C-2G10	[Aib8,22;Gly36]GLP-1(7-37)[(G4S)3(BrAc)]	0.04 nM	0,0008 nM
1187	3166119-E384C-aDNP	[Aib8,22;Gly36]GLP-1(7-37)[(G4S)3(BrAc)]	0.05nM	0,08 nM

FIG. 3B

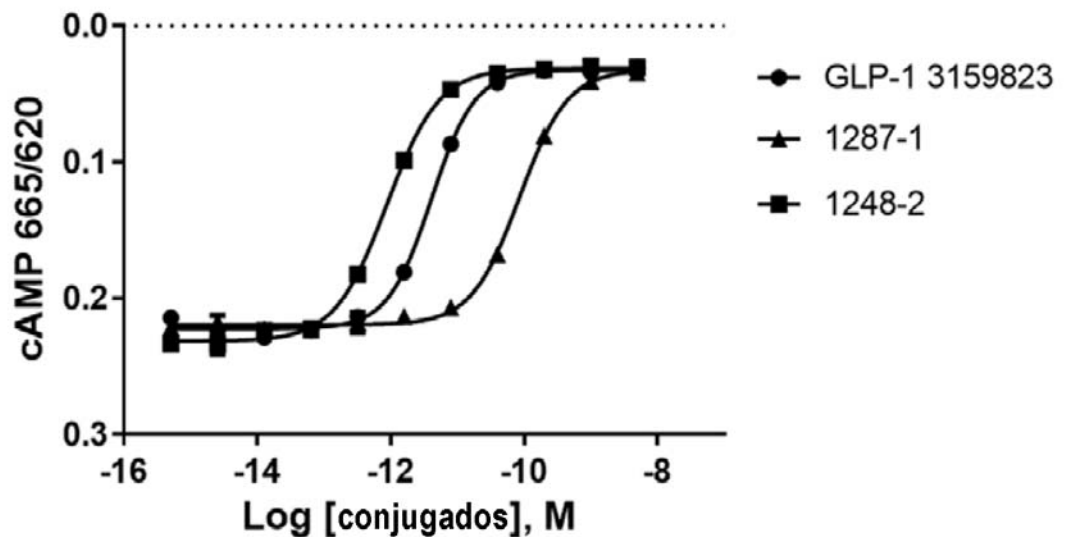
Ensayo cAMP (modo del agonista GLP1) en CHOK1 hGLP1R H20



	GLP-1 3159823	1287-1	1248-2
EC50	1.990e-012	4.963e-011	4.010e-011

FIG. 3C

Ensayo cAMP (modo del agonista GLP1) en CHOK1 hGLP1R/hGIPR M1:



	GLP-1 3159823	1287-1	1248-2
EC50	4.091e-012	8.573e-011	8.793e-013

FIG. 4A

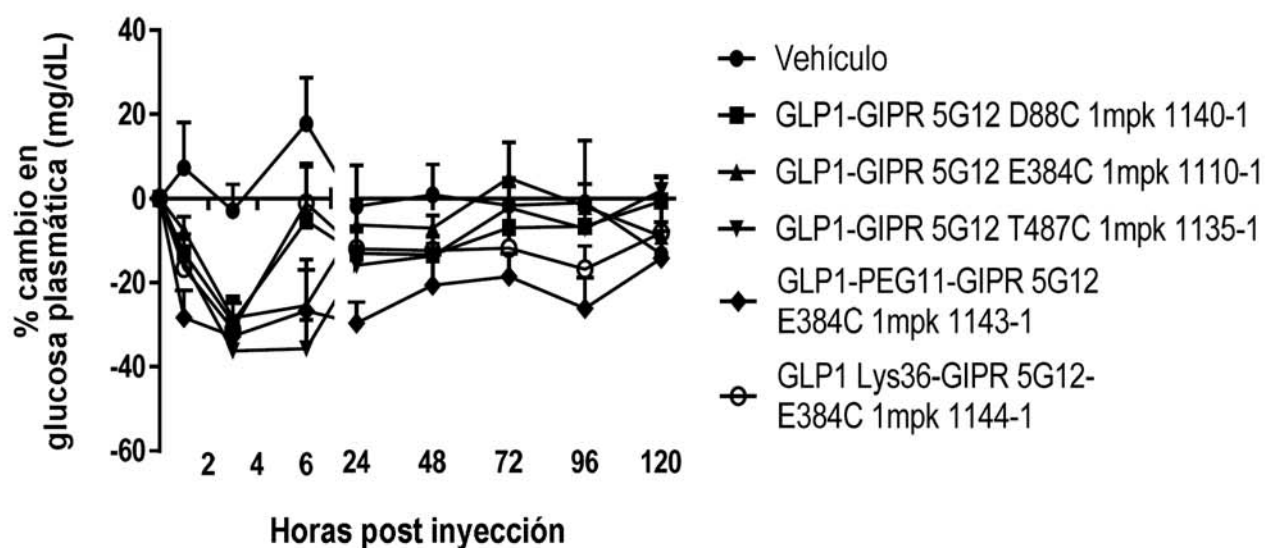


FIG. 4B

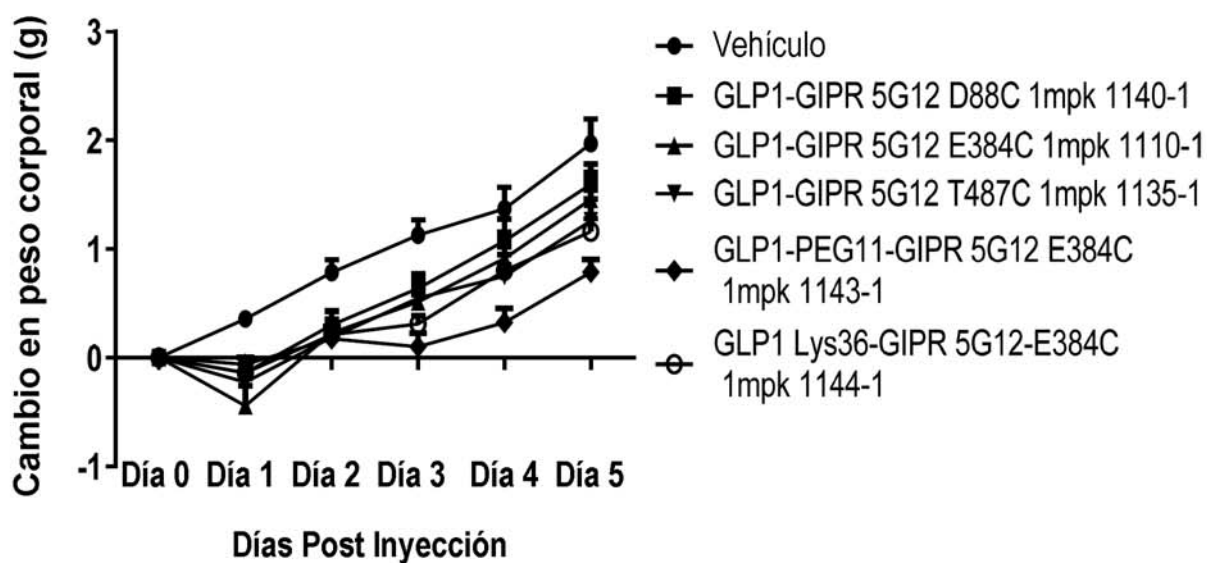


FIG. 4C

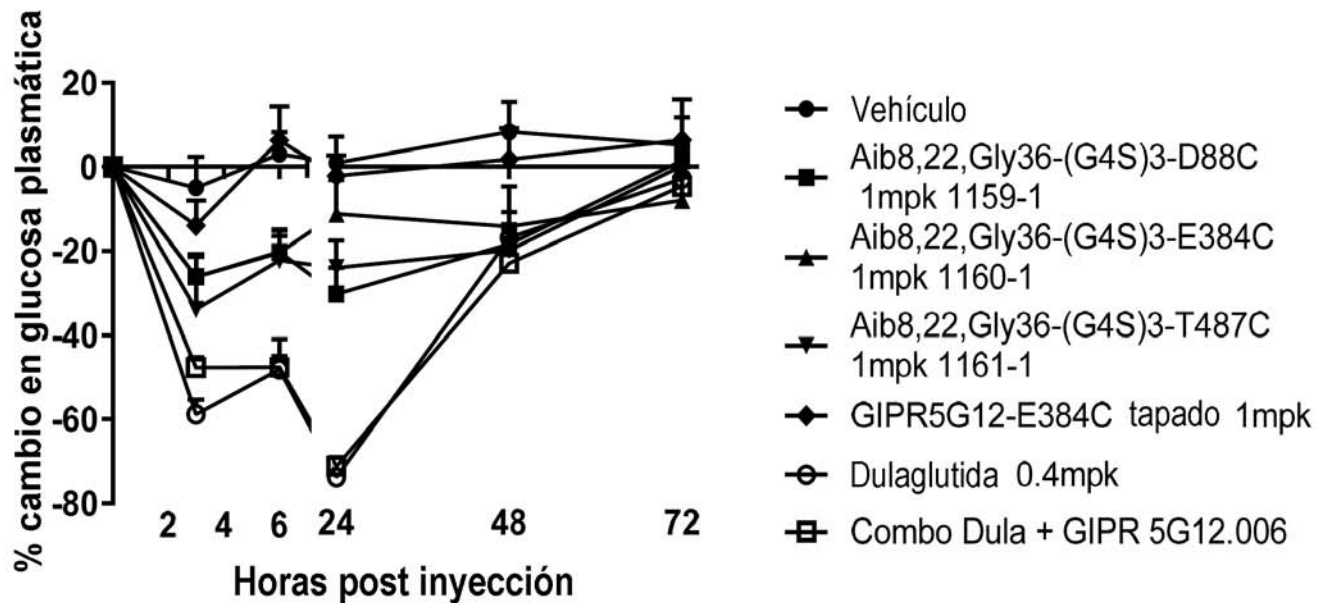


FIG. 4D

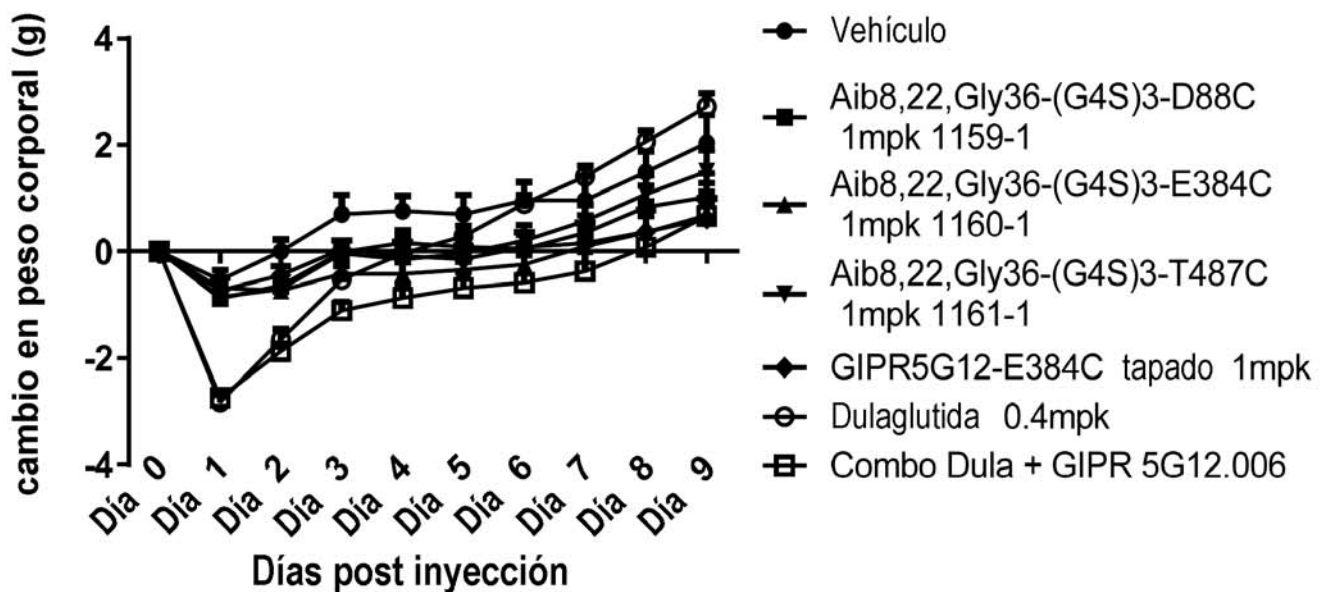


FIG. 4E

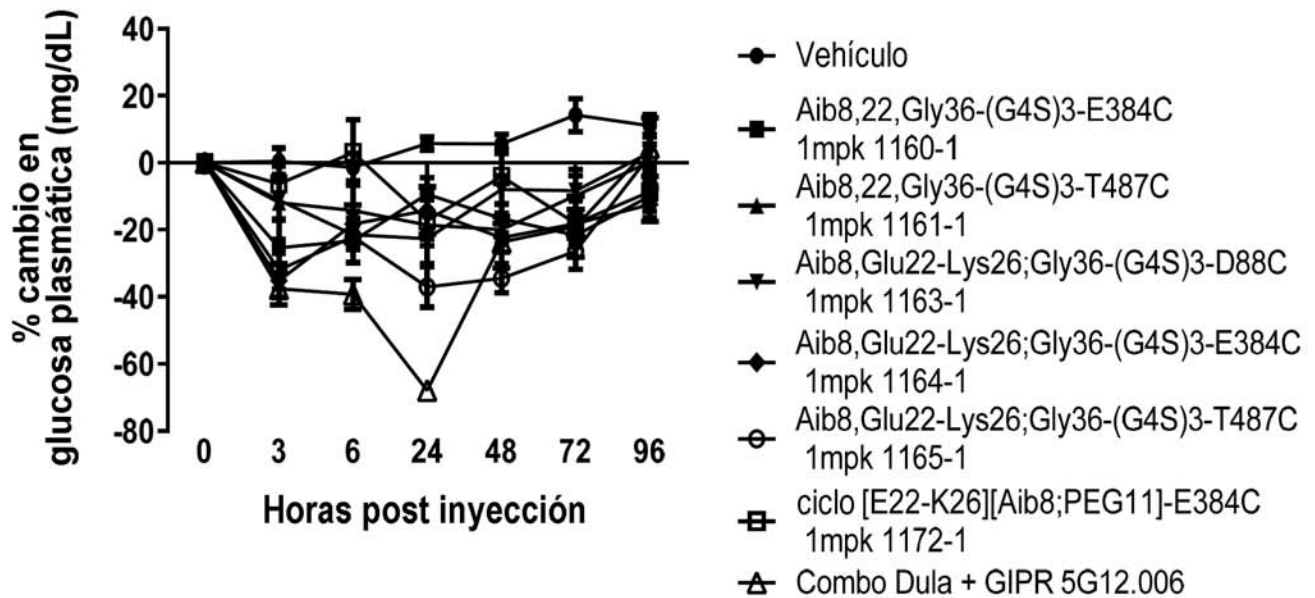


FIG. 4F

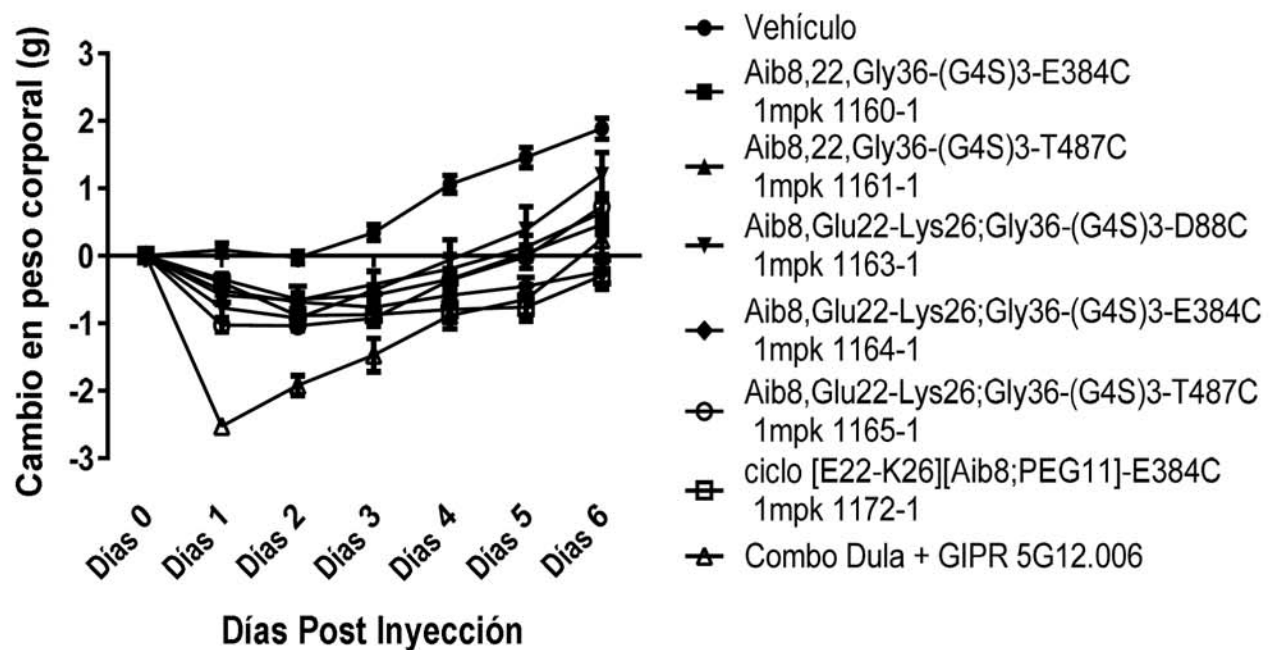


FIG. 4G

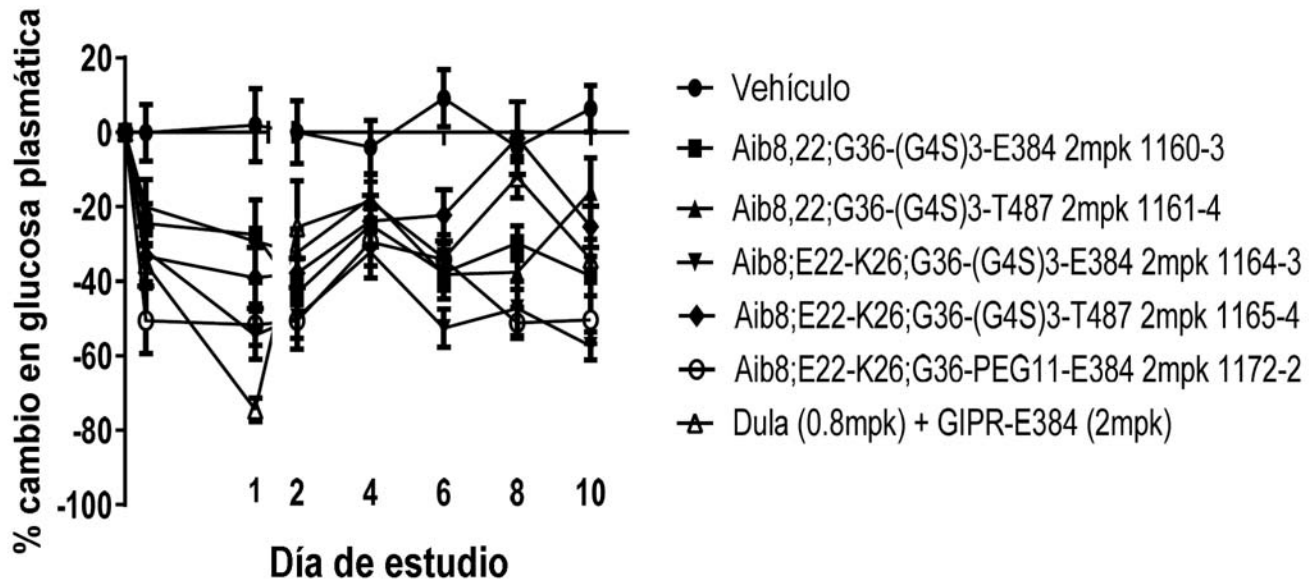


FIG. 4H

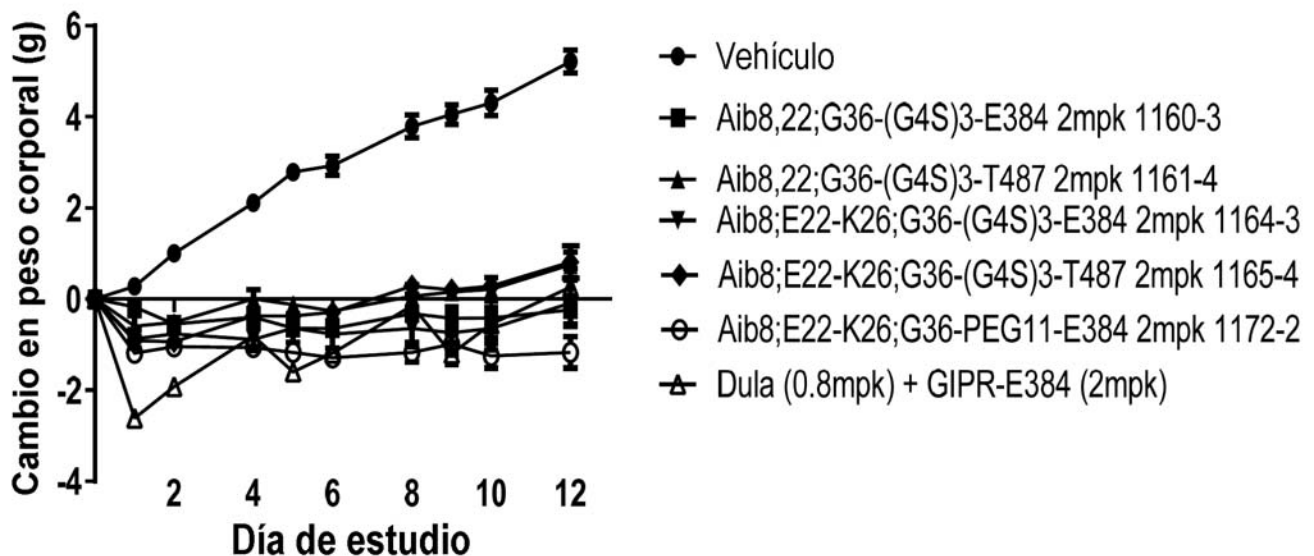


FIG. 4I

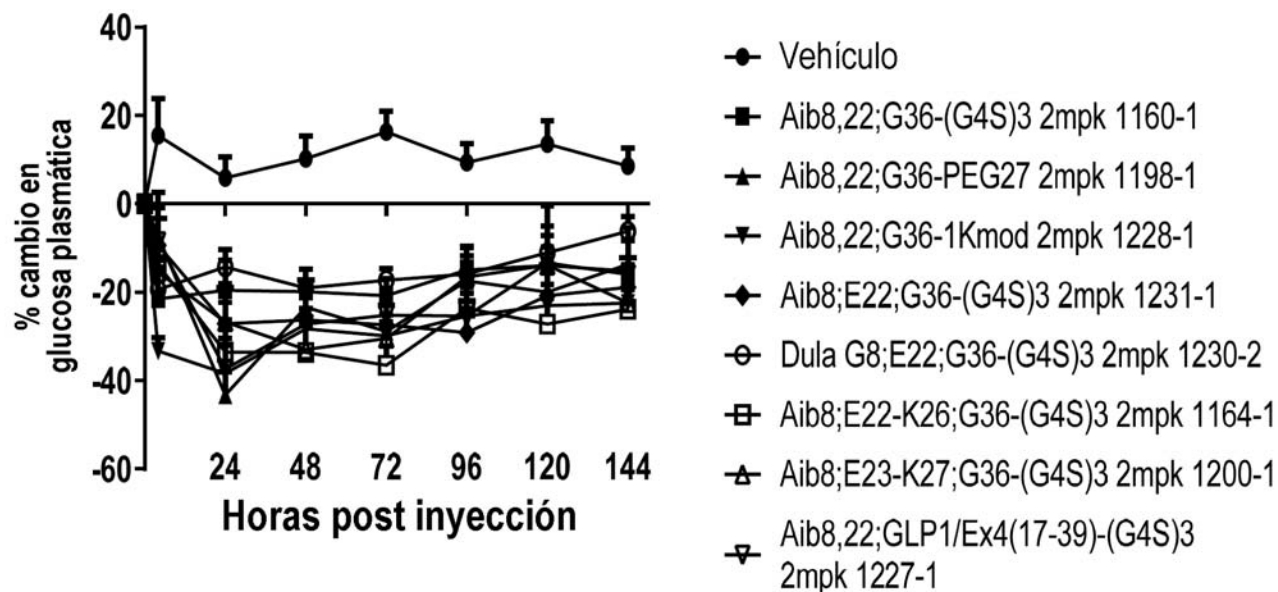


FIG. 4J

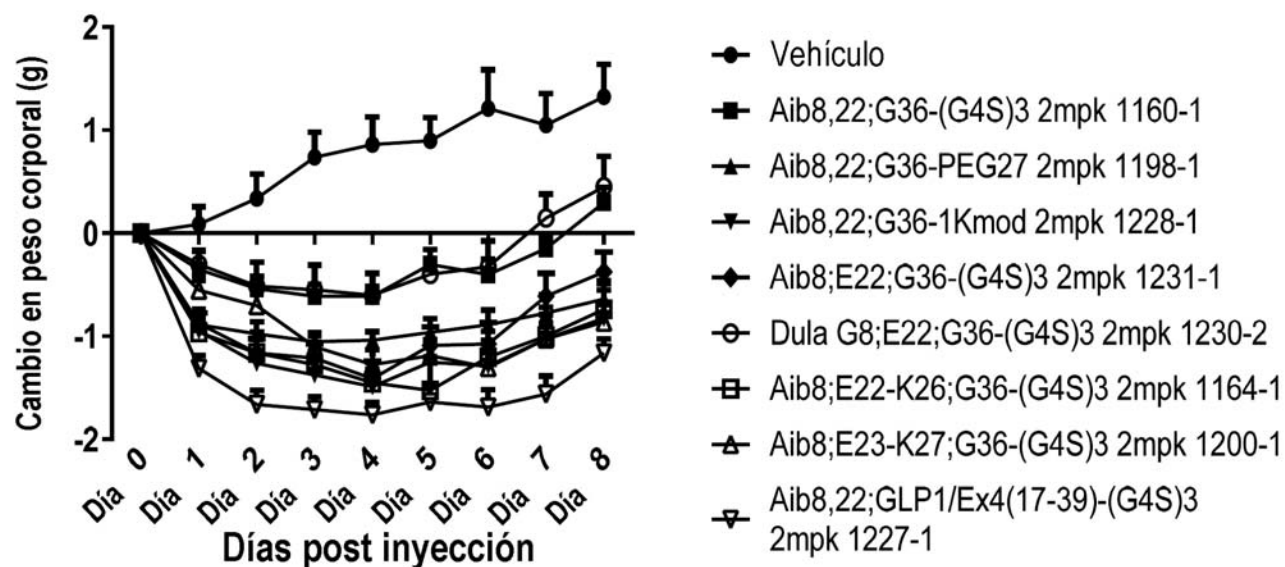


FIG. 4K

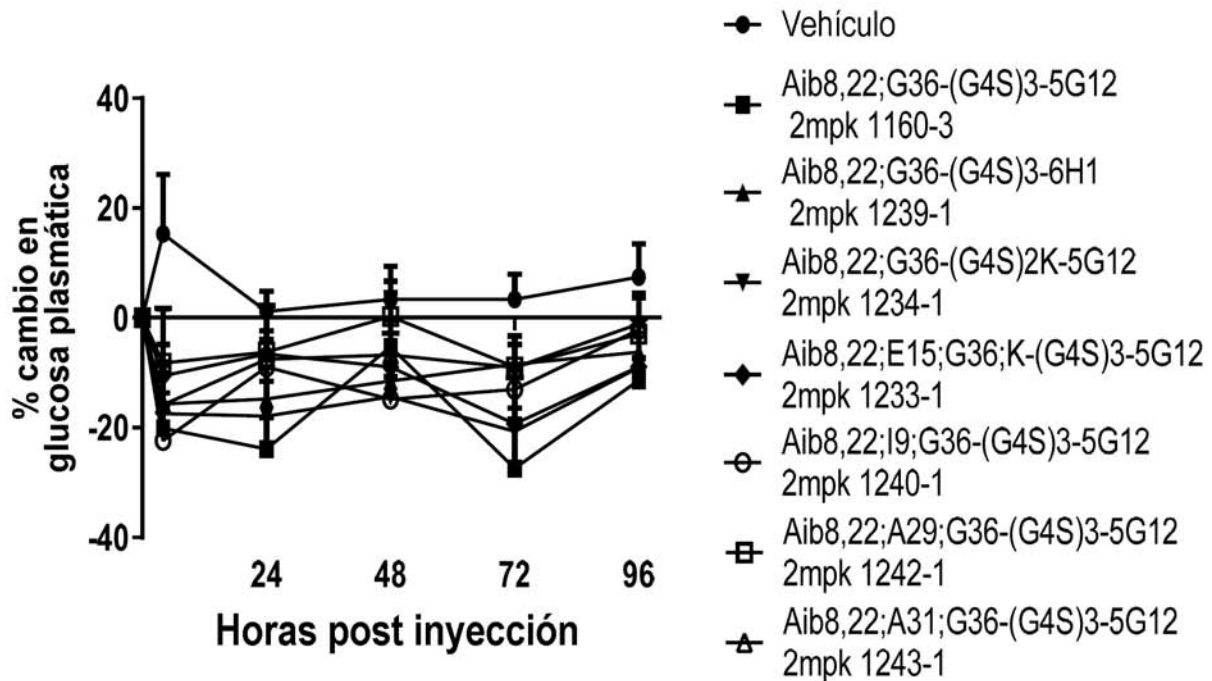


FIG. 4L

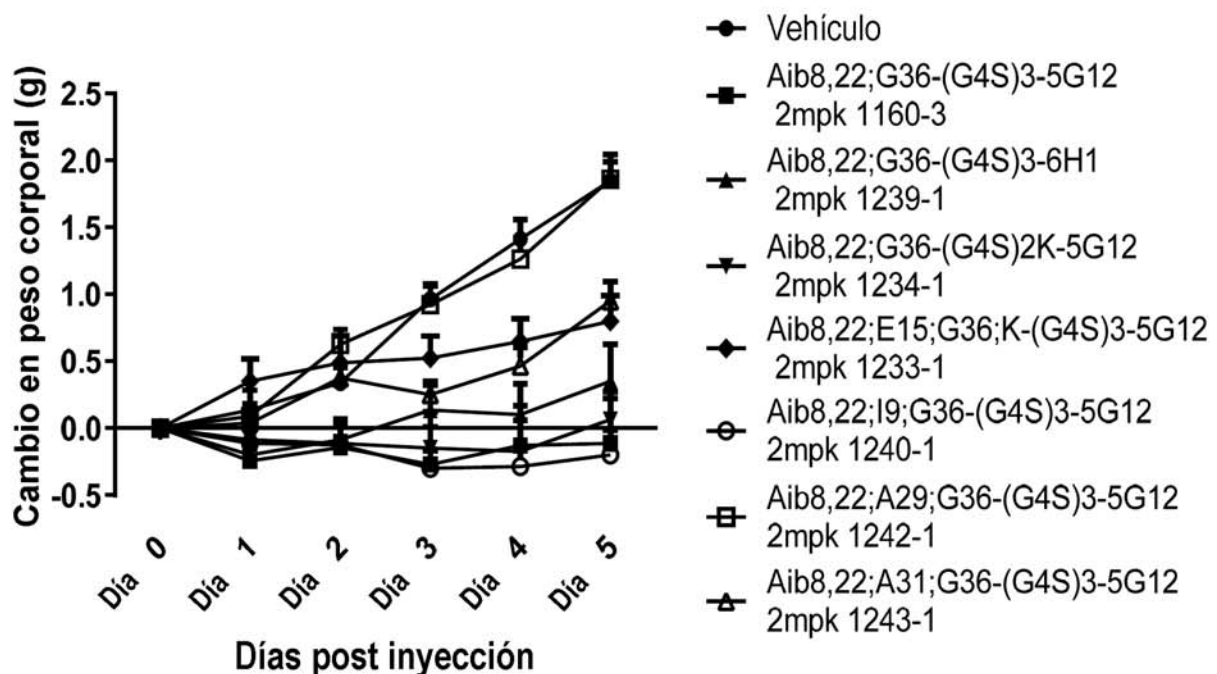


FIG. 4M

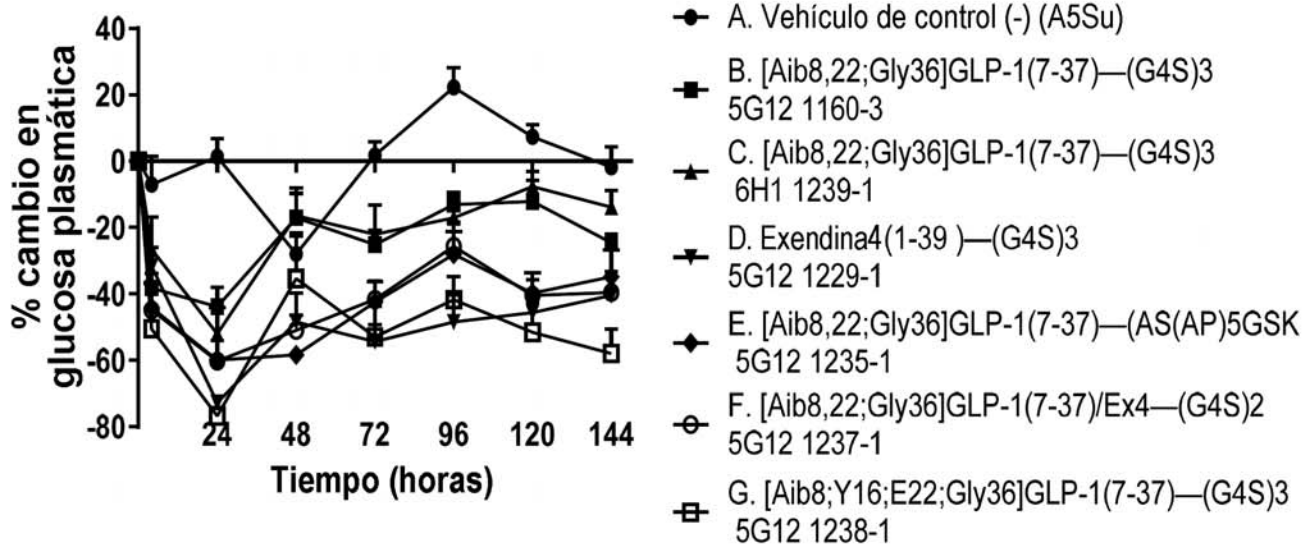


FIG. 4N

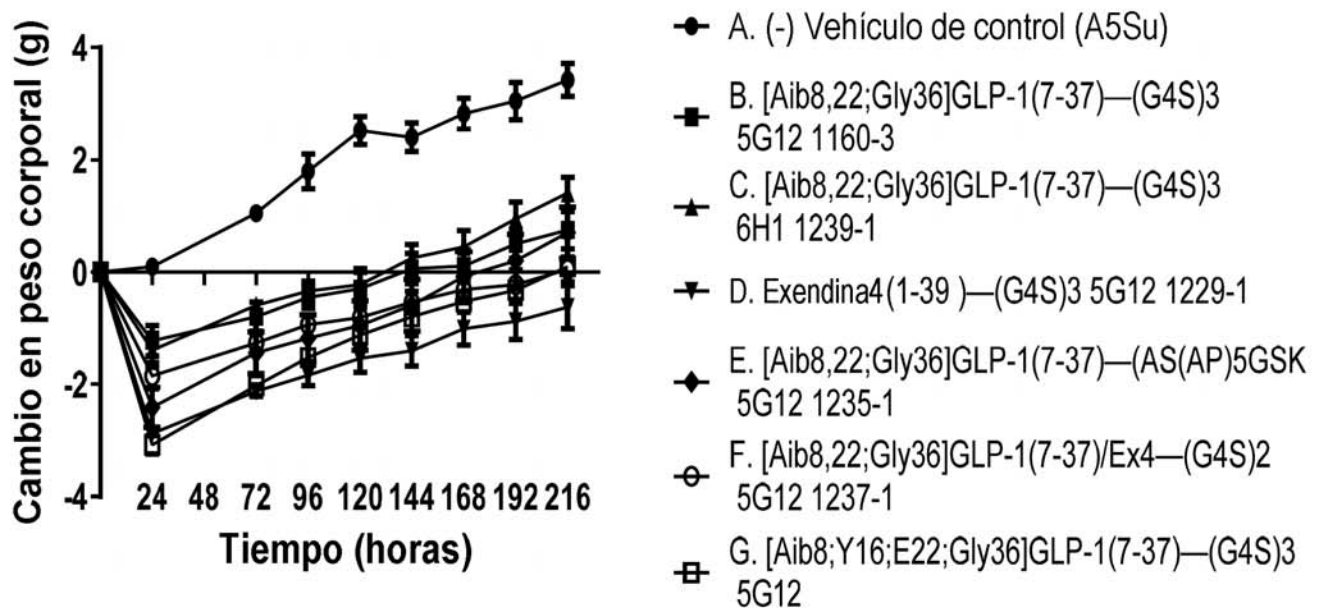


FIG. 4O

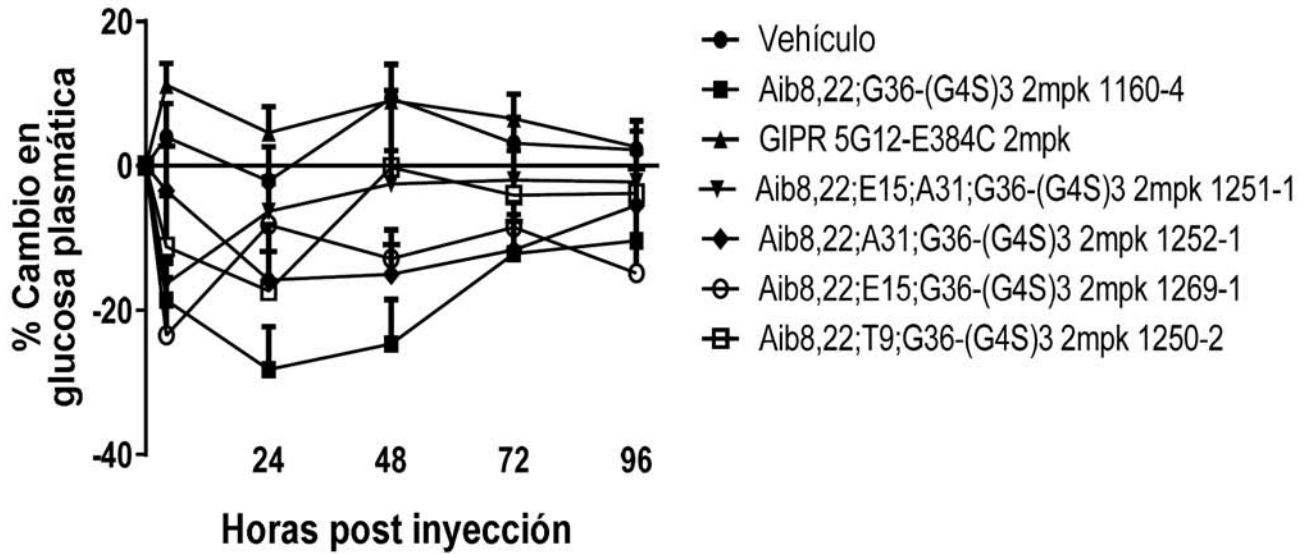


FIG. 4P

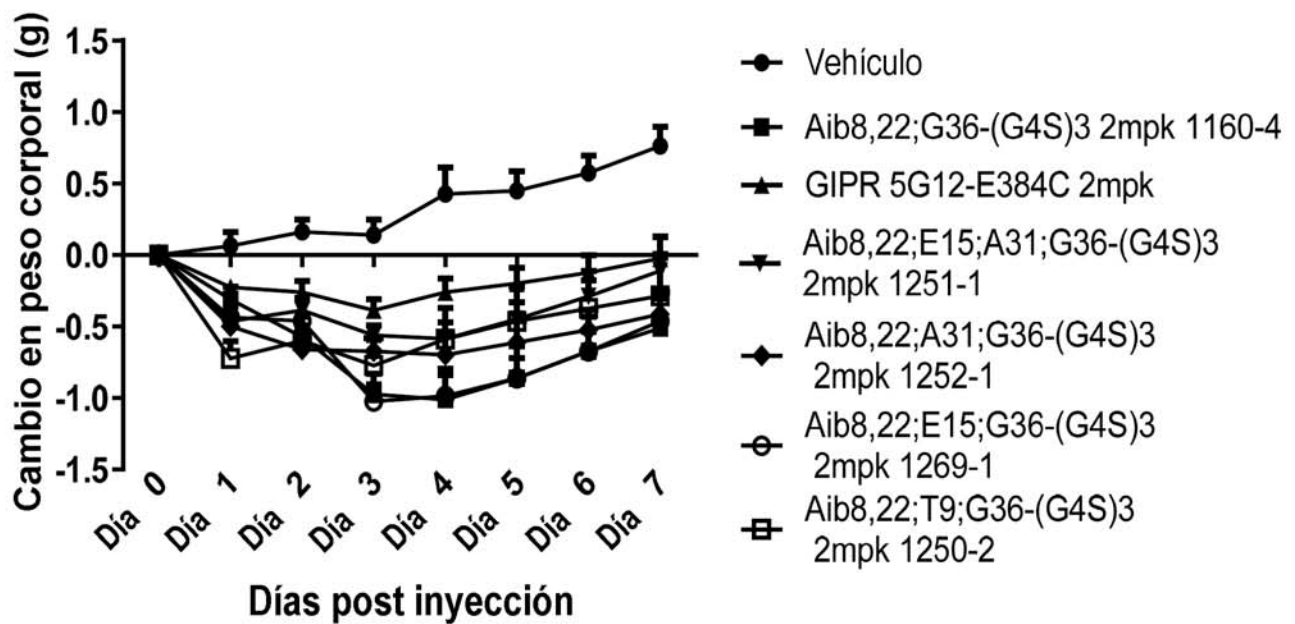


FIG. 4Q

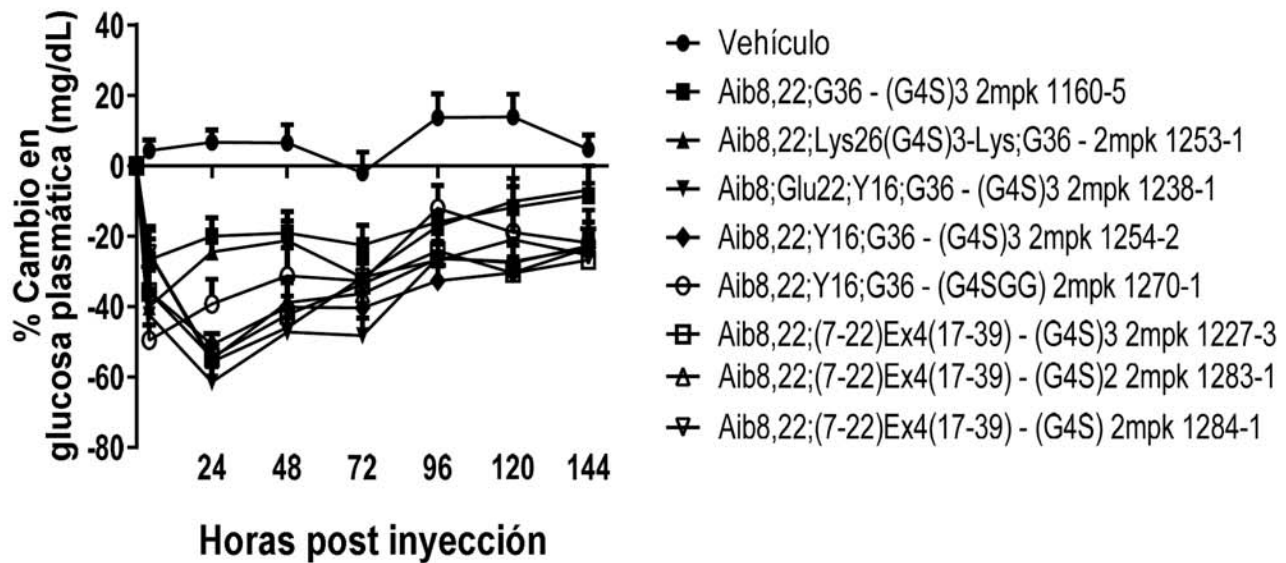


FIG. 4R

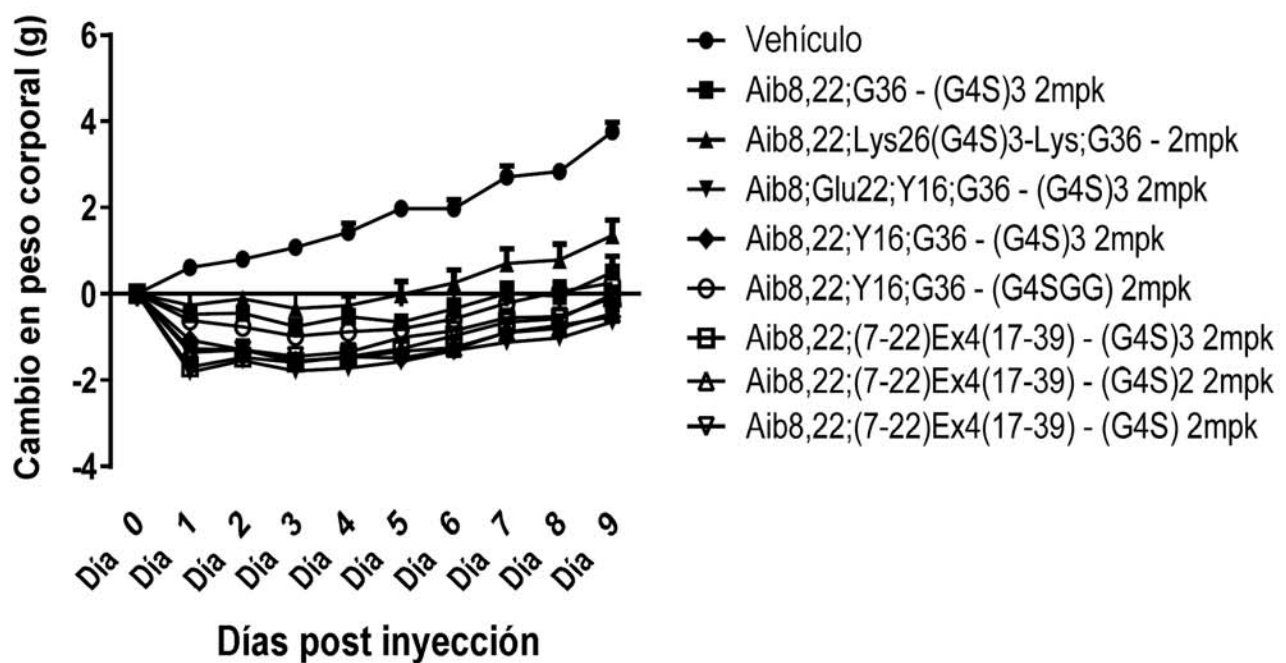


FIG. 5A

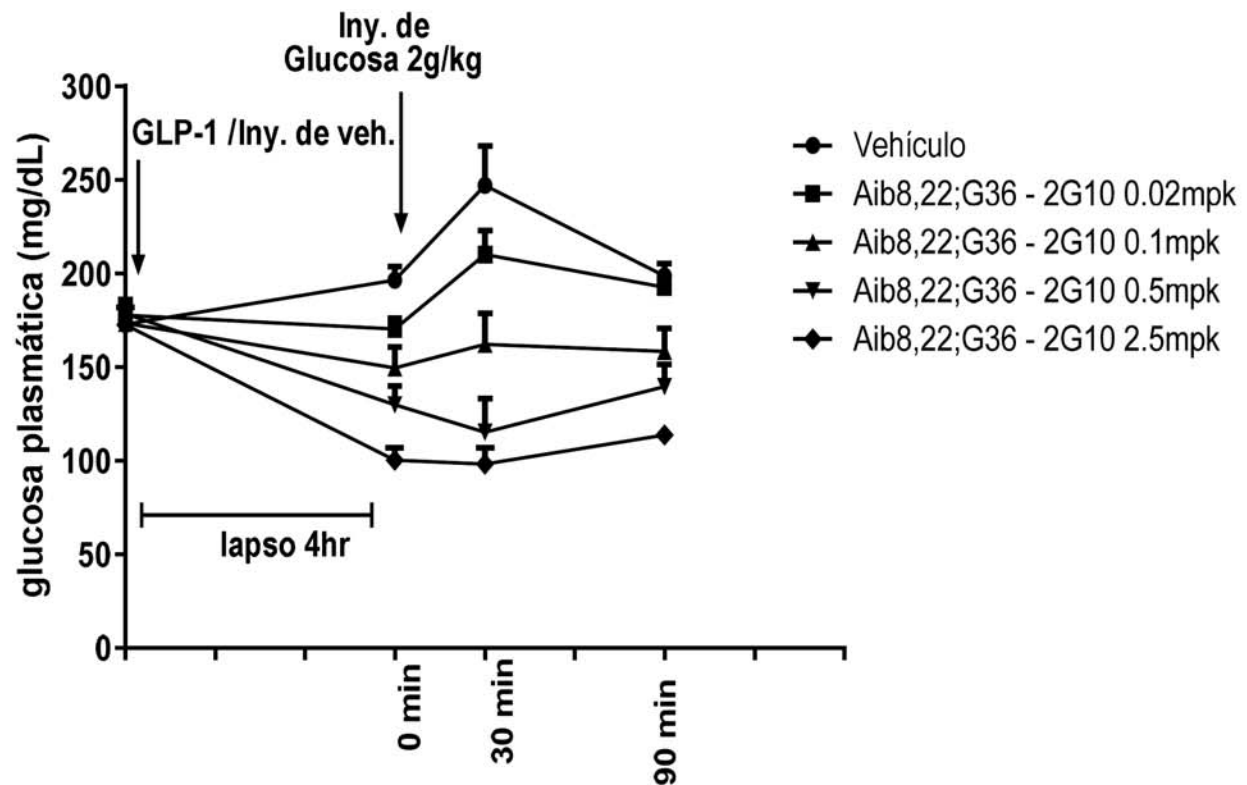


FIG. 5B

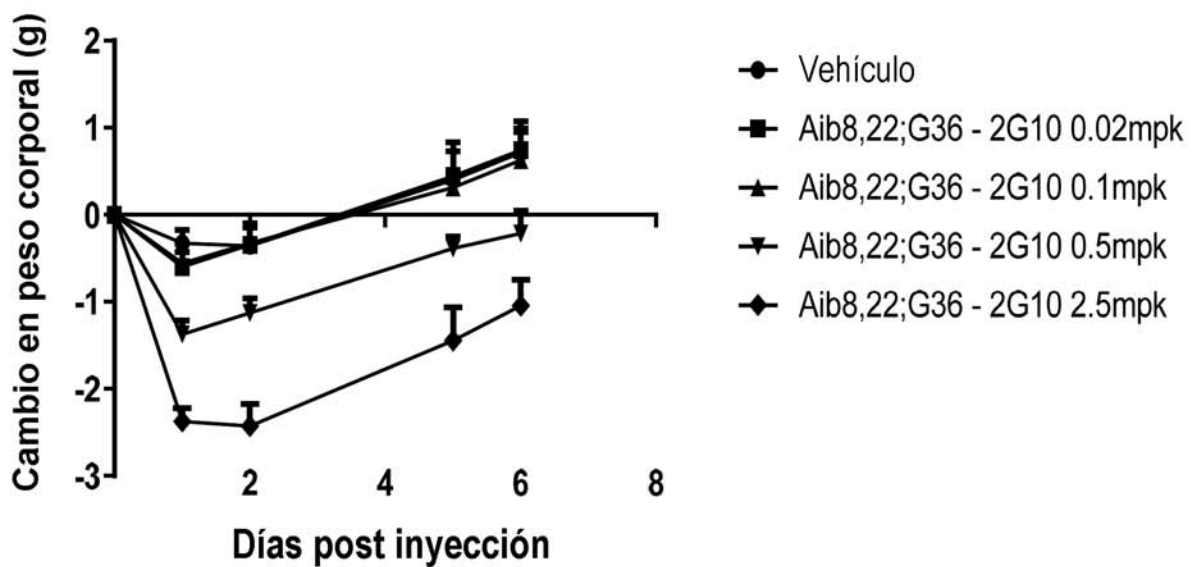


FIG. 5C

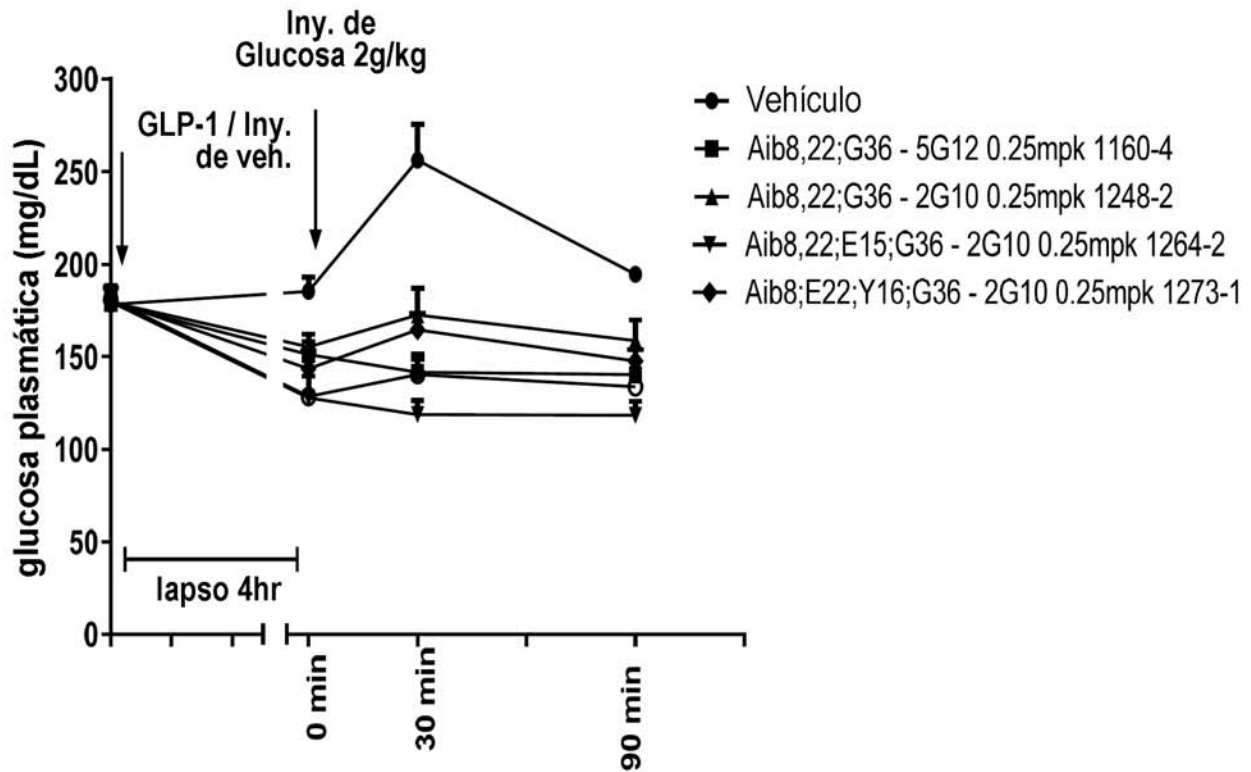


FIG. 5D

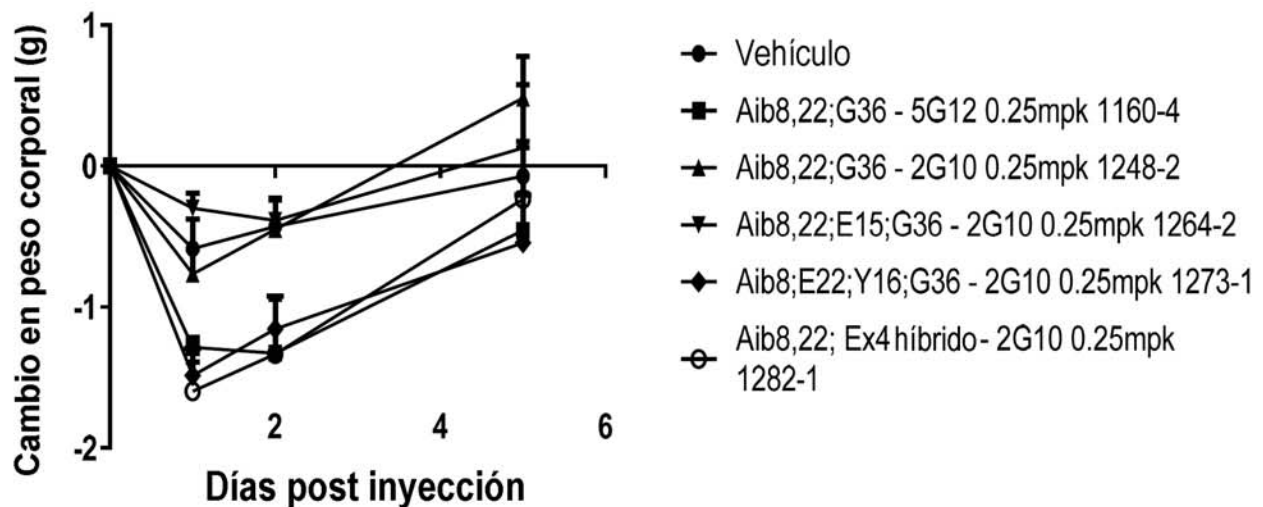


FIG. 6A

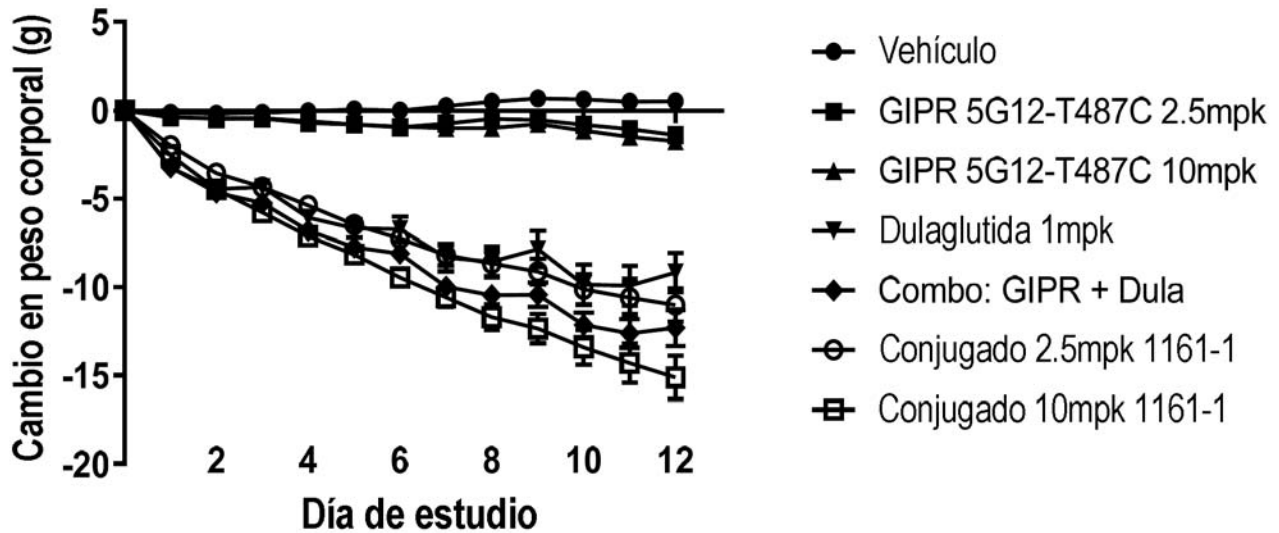


FIG. 6B

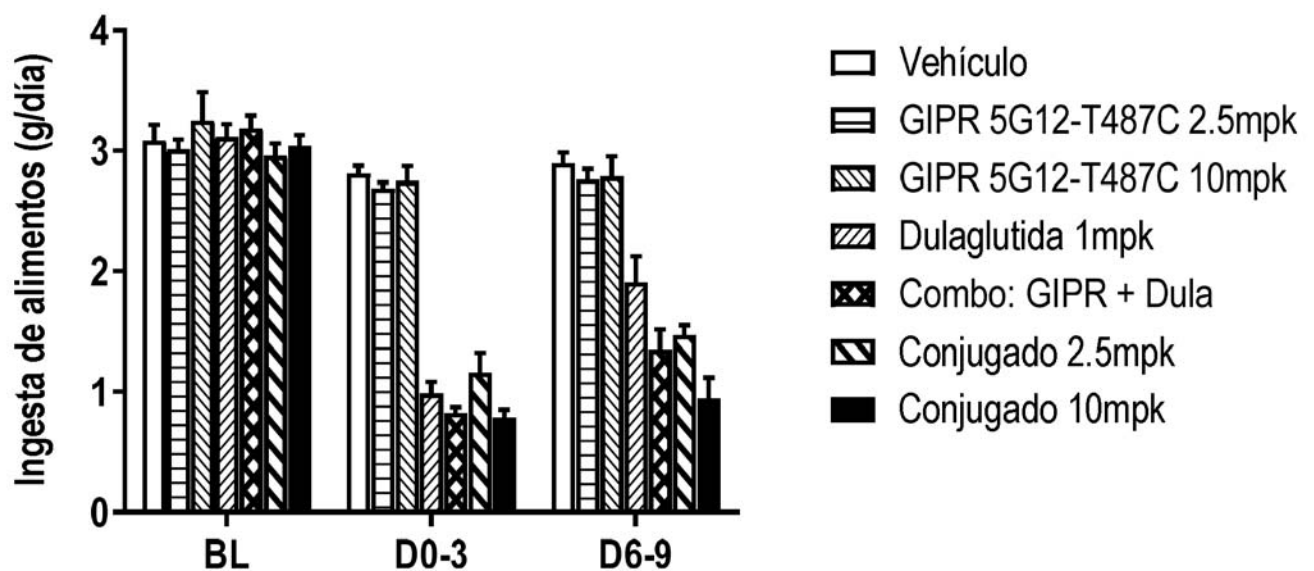
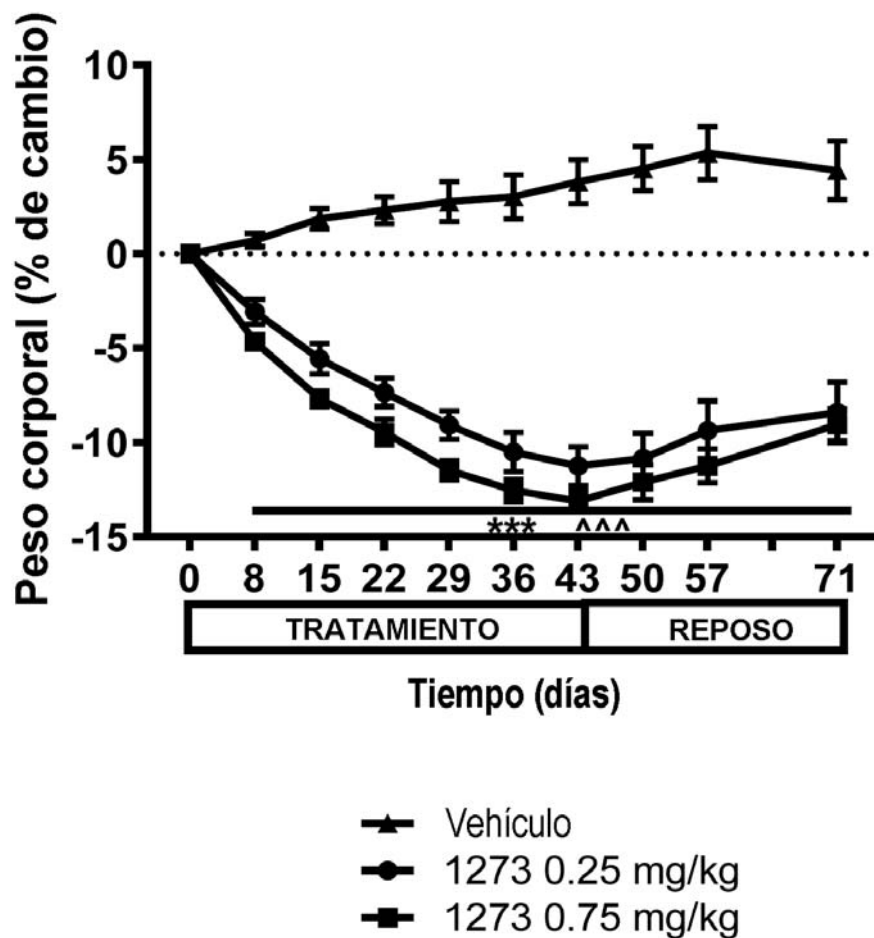
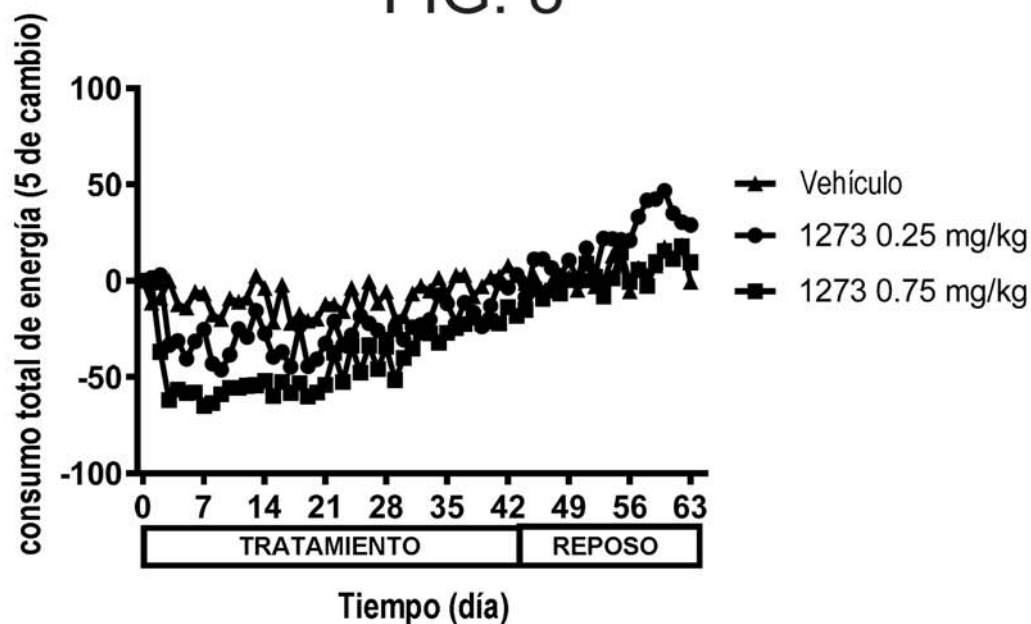


FIG. 7



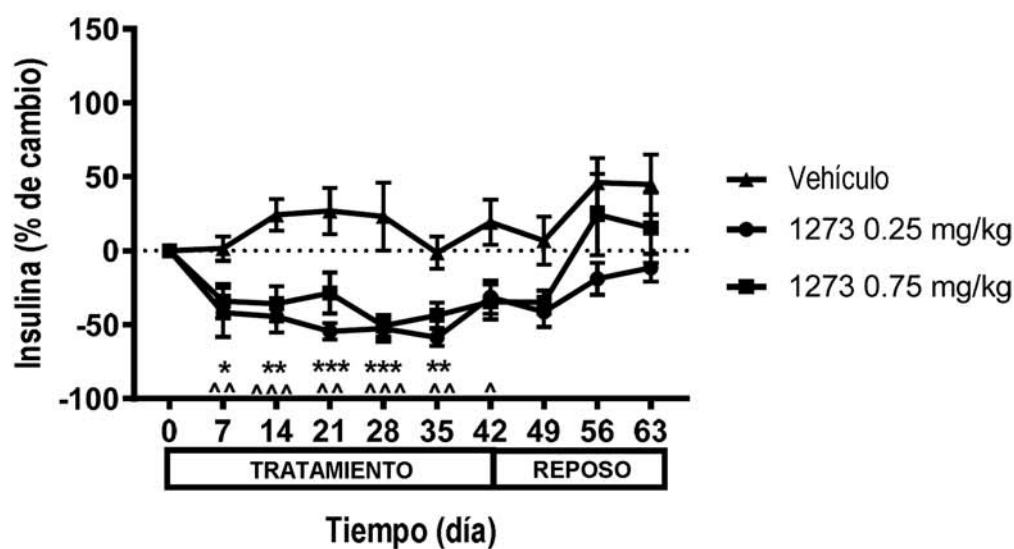
ANCOVA; *** $p < 0.001$ vs vehículo para 0.25 mg/kg; ^^^ $p < 0.001$ vs vehículo para 0.75 mg/kg
Datos representados como promedio de grupo $\pm$ SEM; n=8-9/grupo

FIG. 8



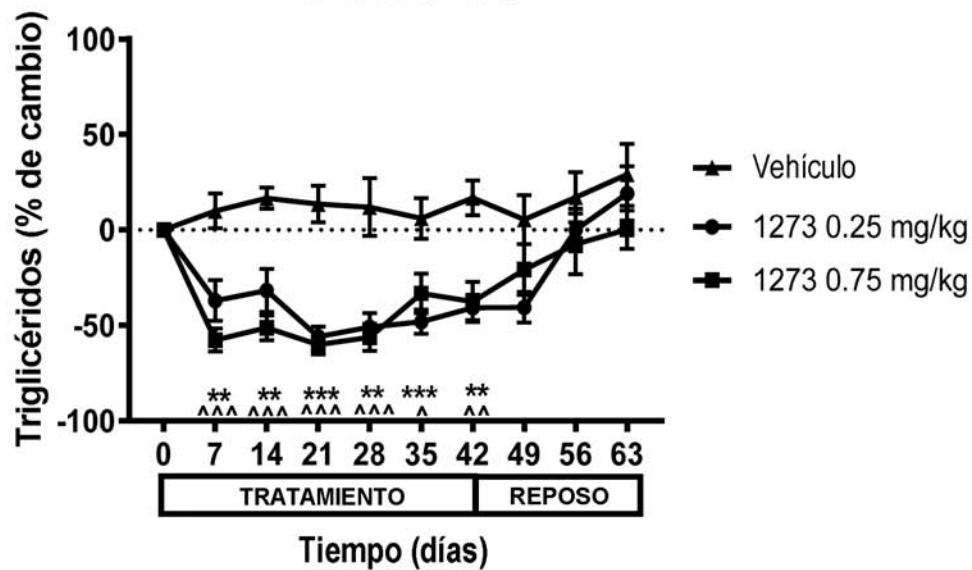
No se realizó un análisis estadístico en el consumo total de energía; no se muestran las barras de error; datos representados como promedio de grupo n=8-9/grupo

FIG. 9



ANCOVA; *p<0.05, **p<0.01, ***p<0.001 vs vehículo para 0.25 mg/kg; ^p<0.05, ^^p<0.01, ^^p<0.001 vs vehículo para 0.75 mg/kg Los datos se representan como promedio de grupo $\pm$ SEM; n=8-9/grupo

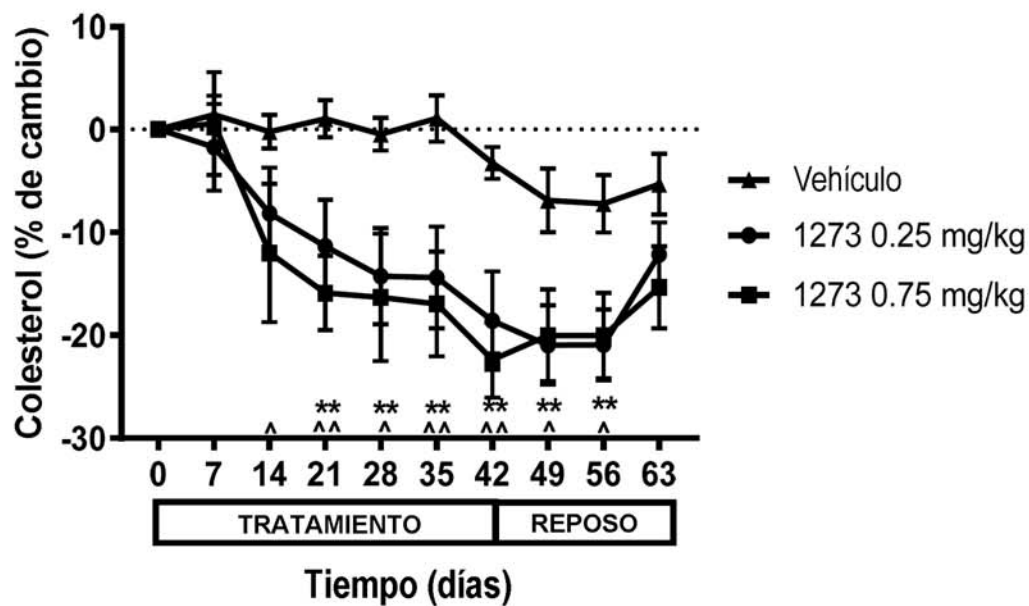
FIG. 10



ANCOVA; **p<0.01, ***p<0.001 vs vehículo para 0.25 mg/kg; ^p<0.05, ^^p<0.01, ^^p<0.001 vs vehículo para 0.75 mg/kg

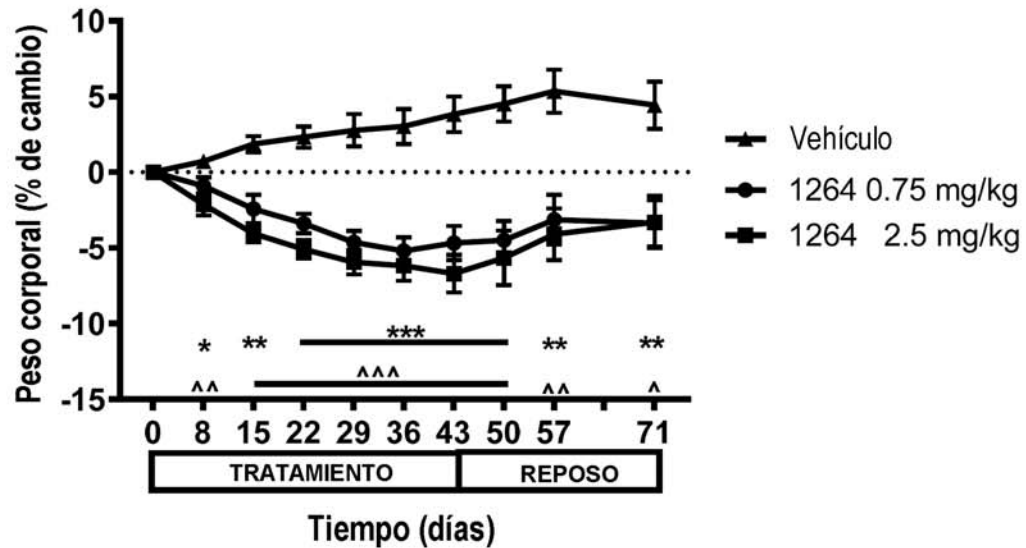
Los datos se representan como promedio de grupo $\pm$ SEM; n=8-9/grupo

FIG. 11



ANCOVA; **p<0.01 vs vehículo para 0.25 mg/kg; ^p<0.05, ^^p<0.01 vs vehículo para 0.75mg/kg Los datos se representan como promedio de grupo $\pm$ SEM; n=8-9/grupo

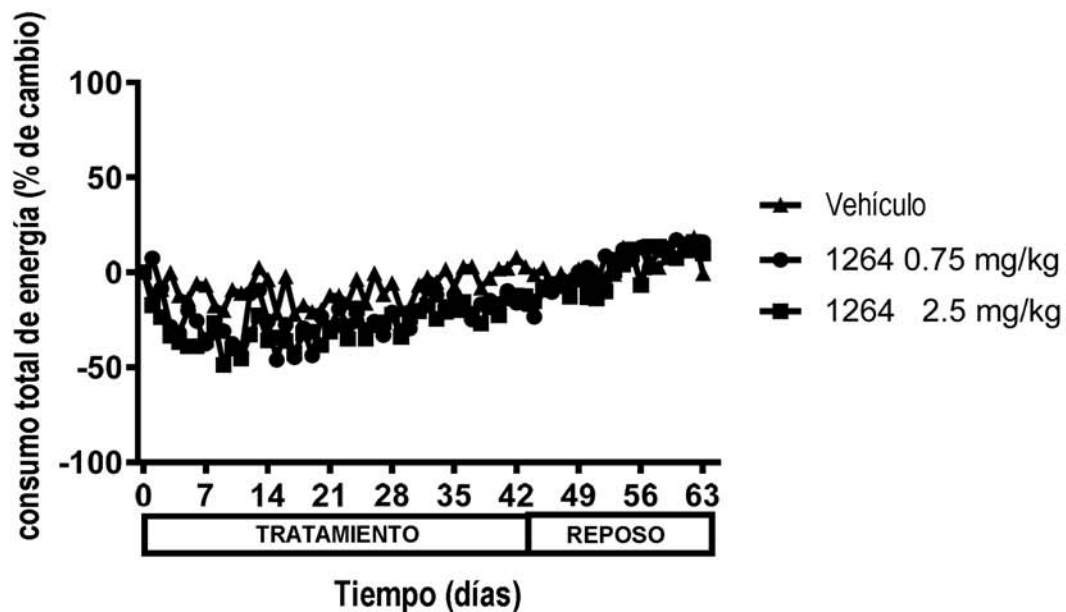
FIG. 12



ANCOVA; *p<0.05, **p<0.01, *** p<0.001 vs vehículo para 0.75 mg/kg; ^p<0.05, ^^p<0.01, ^^^p<0.001 vs vehículo para 2.5 mg/kg

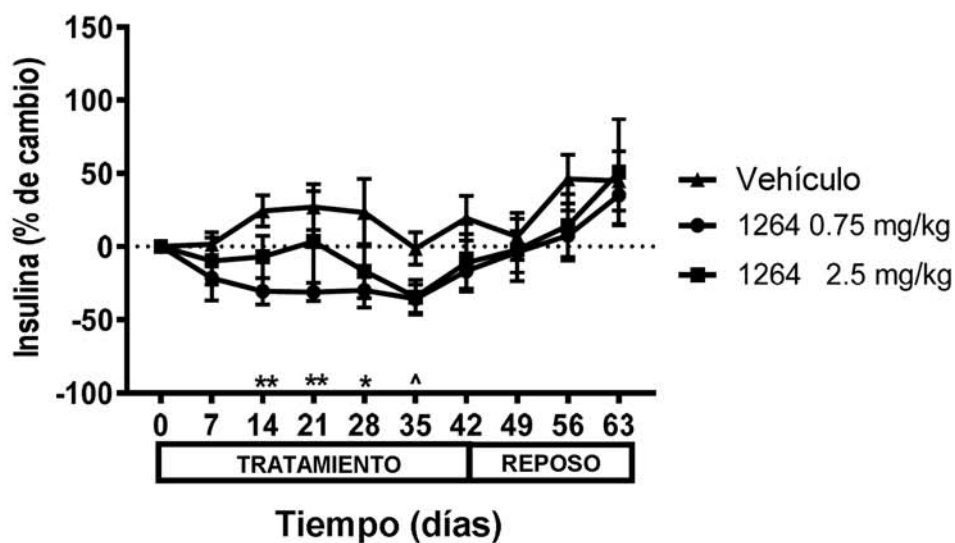
Los datos se representan como promedio de grupo $\pm$ SEM; n=9/grupo

FIG. 13



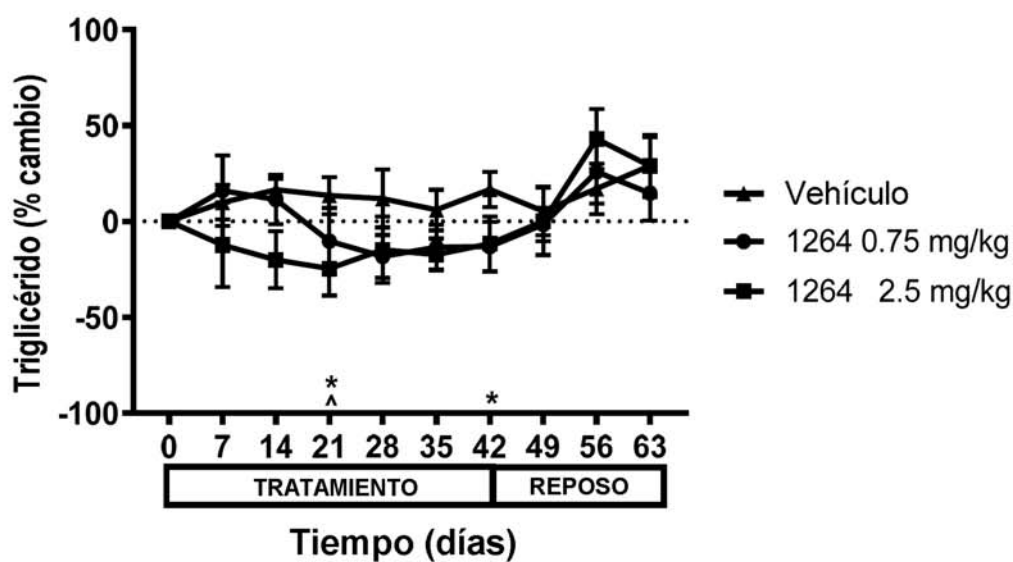
No se realizó análisis estadístico en el consumo total de energía; no se muestran las barras de error; los datos se representan como promedio de grupo $\pm$ SEM; n=9/grupo

FIG. 14



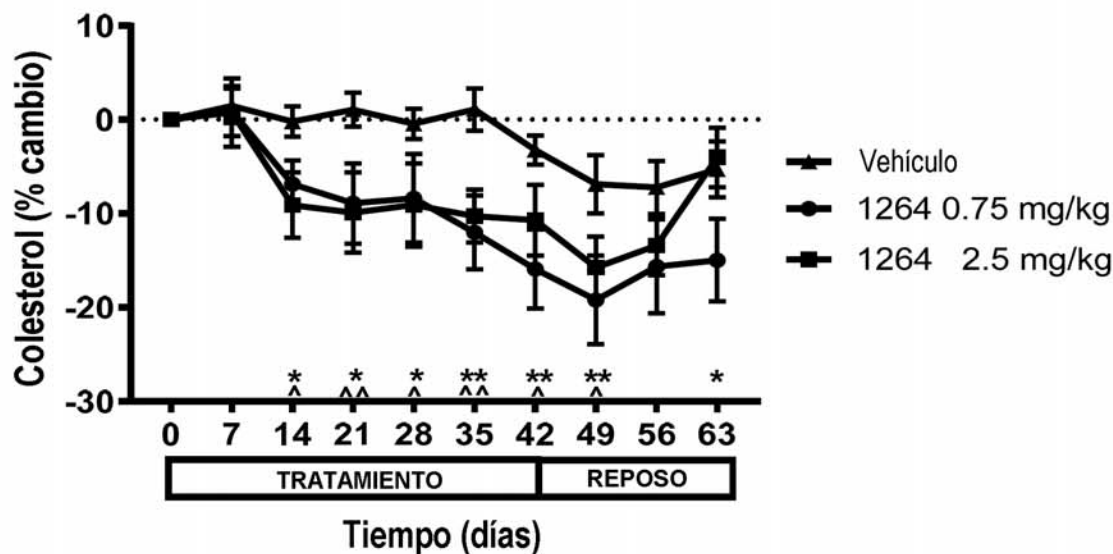
ANCOVA; * $p < 0.05$, ** $p < 0.01$ vs vehículo para 0.75 mg/kg; ^ $p < 0.05$ vs vehículo para 2.5 mg/kg
 Los datos se representan como promedio de grupo $\pm$ SEM; $n=9$ /grupo

FIG. 15



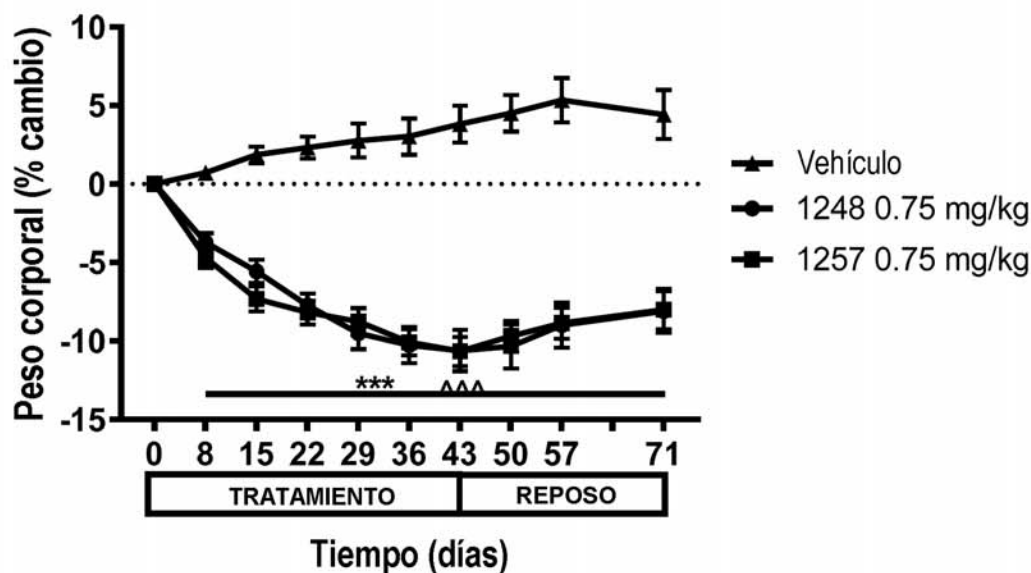
ANCOVA; * $p < 0.05$ vs vehículo para 0.75 mg/kg; ^ $p < 0.05$ vs vehículo para 2.5 mg/kg
 Datos representados como promedio de grupo $\pm$ SEM; $n=9$ /grupo

FIG. 16



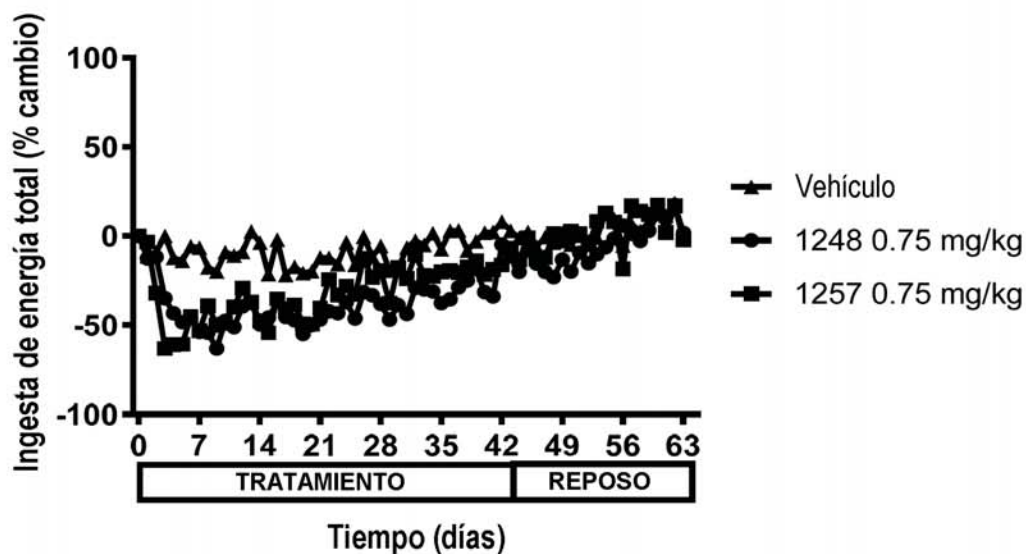
ANCOVA; * $p < 0.05$, ** $p < 0.01$ vs vehículo para 0.75 mg/kg; ^ $p < 0.05$, ^^ $p < 0.01$ vs vehículo para 2.5 mg/kg Datos representados como promedio de grupo $\pm$ SEM; $n = 9$ /grupo

FIG. 17



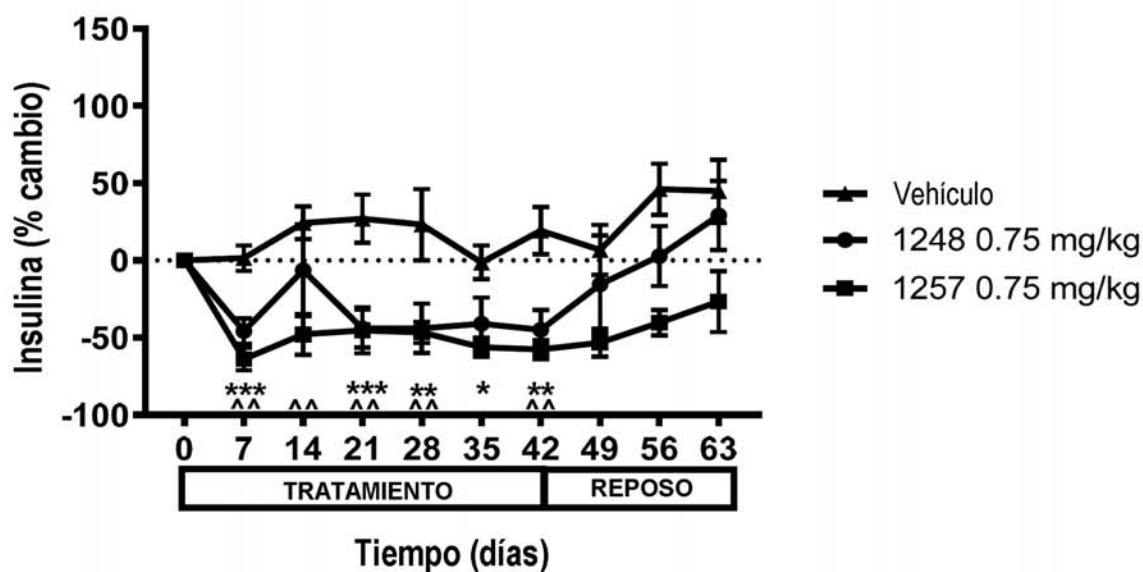
ANCOVA; *** $p < 0.001$ vs vehículo para 1248 0.75 mg/kg; ^^ $p < 0.001$ vs vehículo para 1257 0.75 mg/kg Datos representados como promedio de grupo $\pm$ SEM; $n = 7-10$ /grupo

FIG. 18



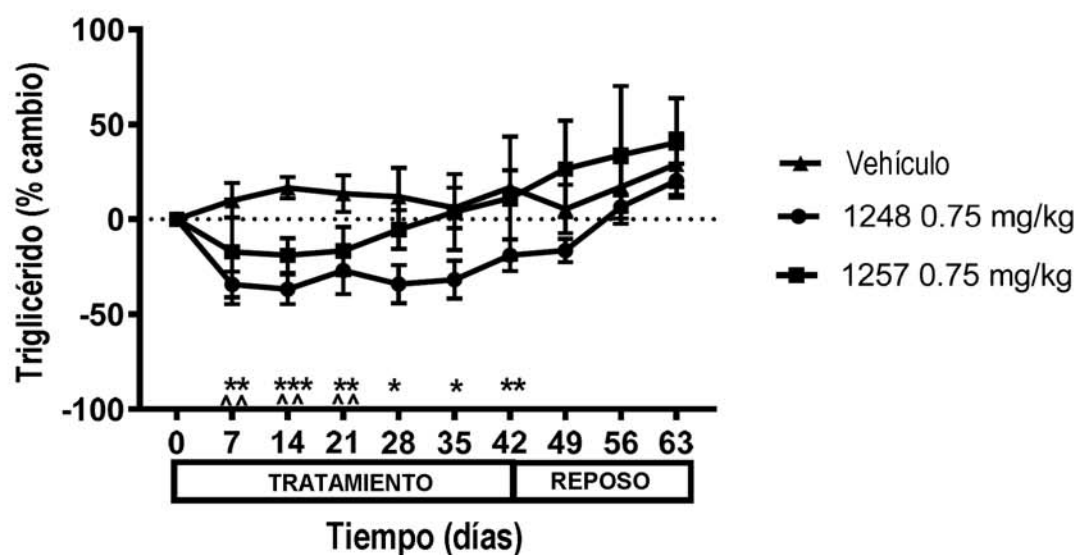
ANCOVA; *** $p < 0.01$ vs vehículo para 1248 0.75 mg/kg; ^^ $p < 0.001$ vs vehículo para 1257 0.75 mg/kg. Datos representados como promedio de grupo $\pm$ SEM; $n = 7-10$ /grupo

FIG. 19



ANCOVA; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs vehículo para 1248 0.75 mg/kg; ^^ $p < 0.01$ vs vehículo para 1257 0.75 mg/kg. Datos representados como promedio de grupo $\pm$ SEM; $n = 7-10$ /grupo

FIG. 20

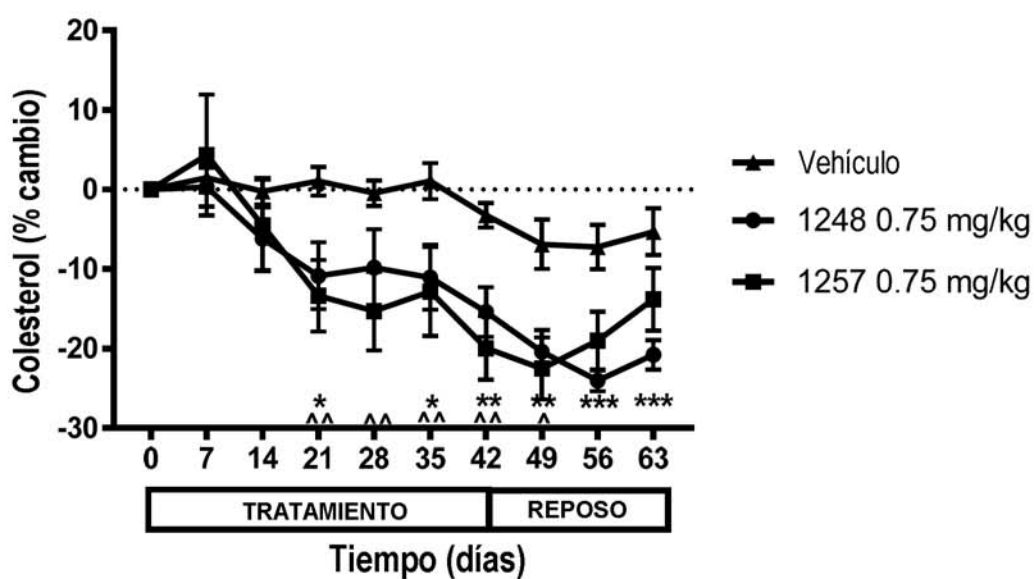


ANCOVA; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs vehículo para 1248 0.75 mg/kg;

^^ $p < 0.01$ vs vehículo para 1257 0.75 mg/kg

Datos representados como promedio de grupo $\pm$ SEM; $n=7-10$ /grupo

FIG. 21

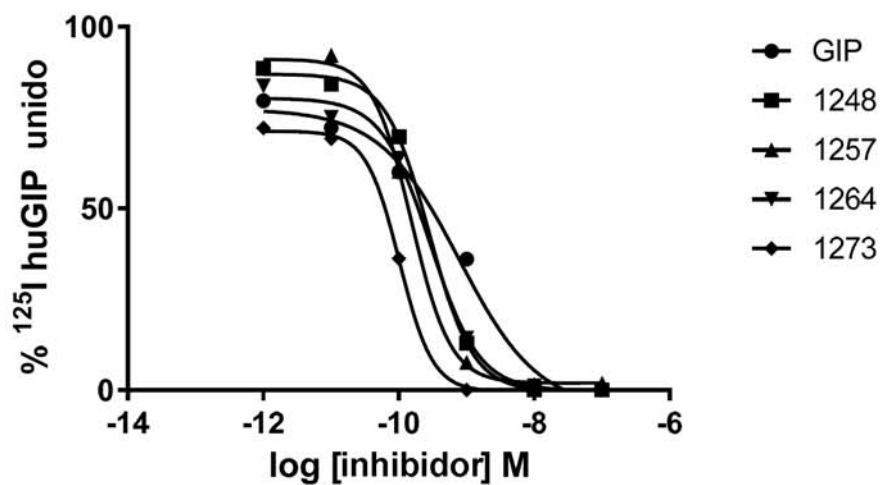


ANCOVA; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs vehículo para 1248 0.75 mg/kg; ^ $p < 0.05$,

^^ $p < 0.01$ vs vehículo para 1257 0.75 mg/kg

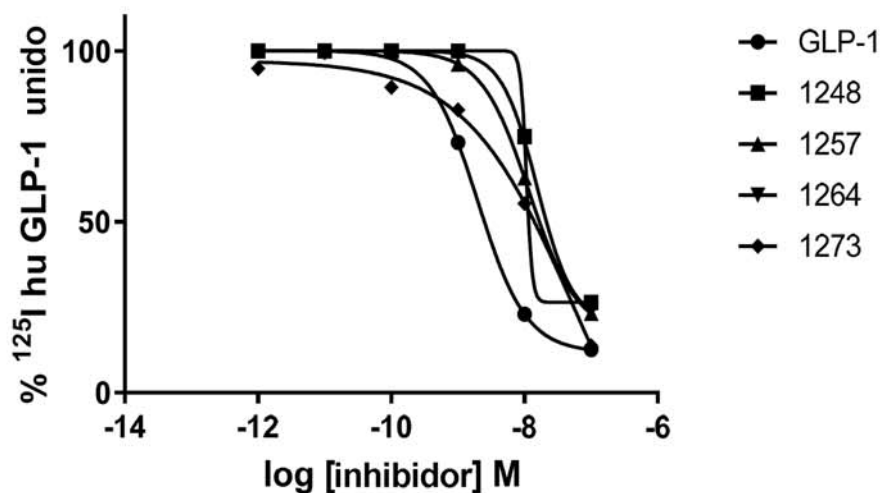
Datos representados como promedio de grupo $\pm$ SEM; $n=7-10$ /grupo

FIG. 22A

Ensayo de unión de radioligandos ^{125}I huGIP

	GIP	1248	1257	1264	1273
IC ₅₀	7.788e-010	2.806e-010	1.539e-010	2.928e-010	1.021e-010

FIG. 22B

Ensayo de unión de radioligandos ^{125}I huGLP-1

	GLP-1	1248	1257	1264	1273
IC ₅₀	1.995e-009	1.069e-008	1.174e-008	1.548e-008	5.627e-008

FIG. 24A

Internalización de GLP1R en células CHOK1 GIPR/GLP-1R M1

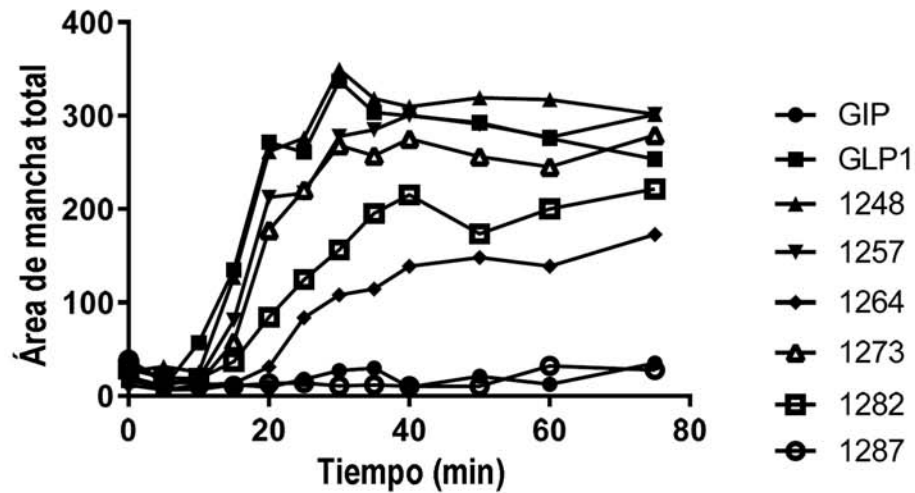
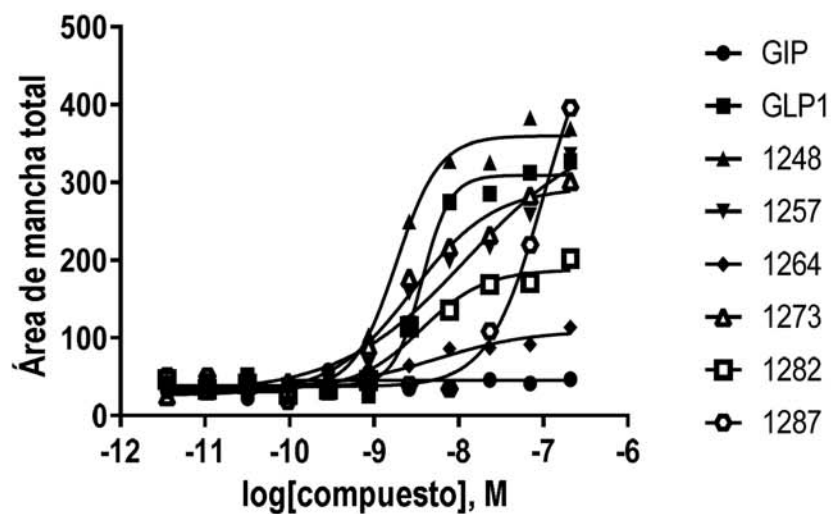


FIG. 24B

Internalización de GLP-1R en células CHOK1 GIPR/GLP-1R M1



	GIP	GLP1	1248	1257	1264	1273	1282	1287
EC50	~ 9.480e-011	3.689e-009	1.834e-009	1.235e-008	5.348e-009	2.830e-009	3.606e-009	1.033e-007

FIG. 25A

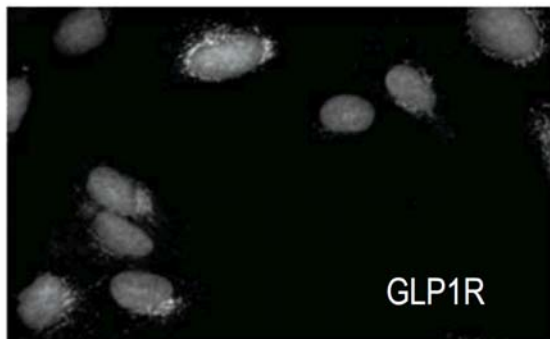


FIG. 25B

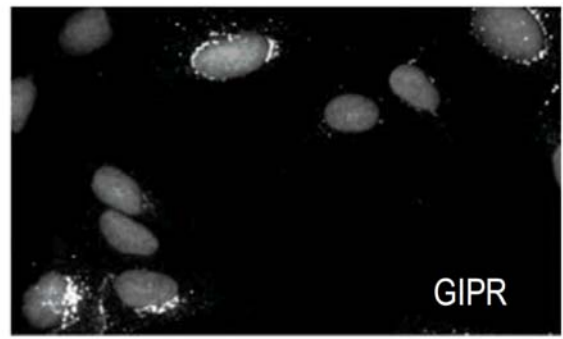


FIG. 25C

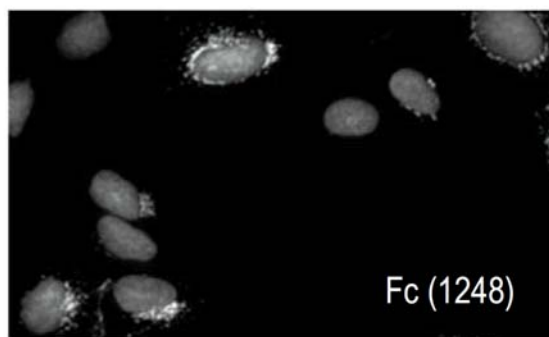


FIG. 25D

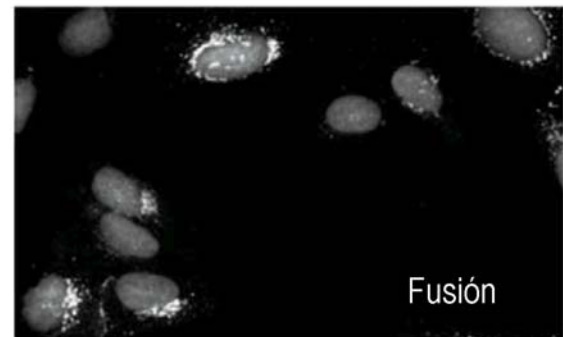


FIG. 26A

Efectos de la inhibición de la internalización del receptor en la actividad de cAMP inducida por 1248

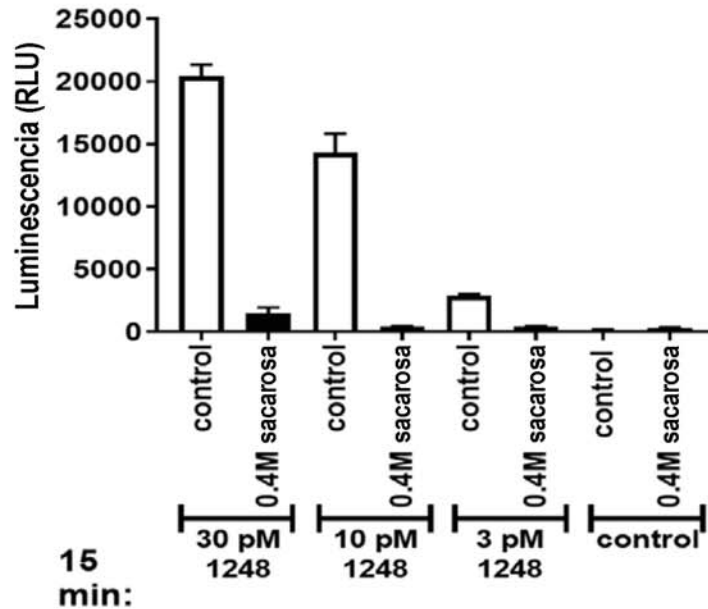
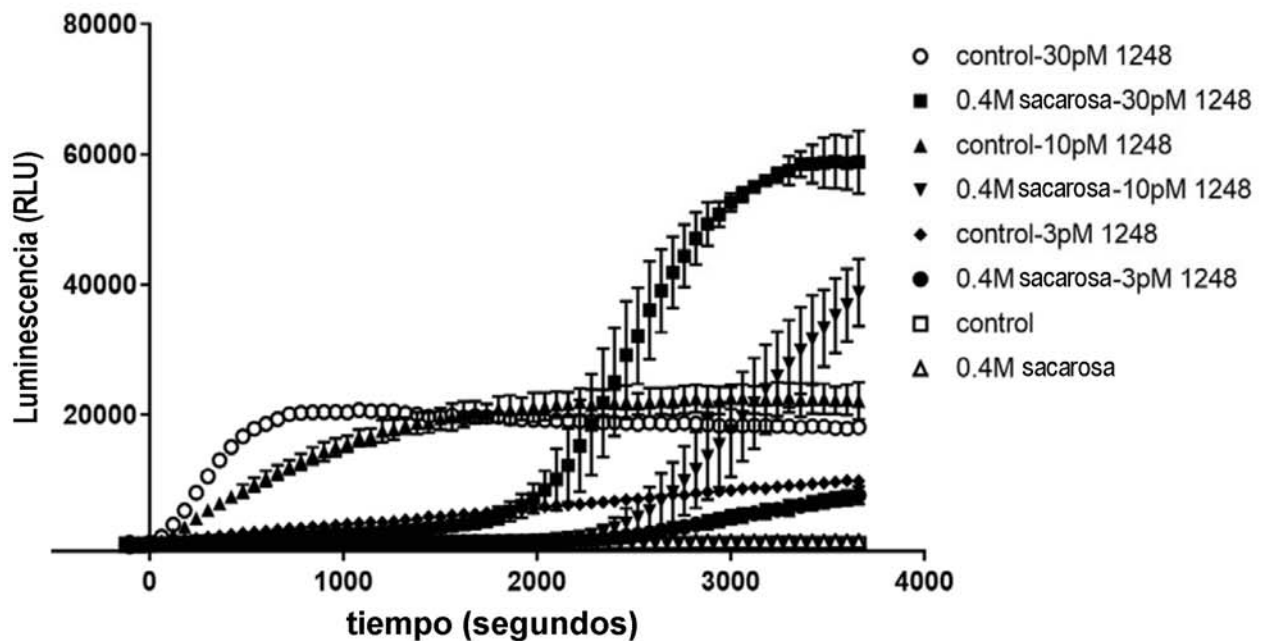


FIG. 26B

ensayo de cAMP GloSensor
1248



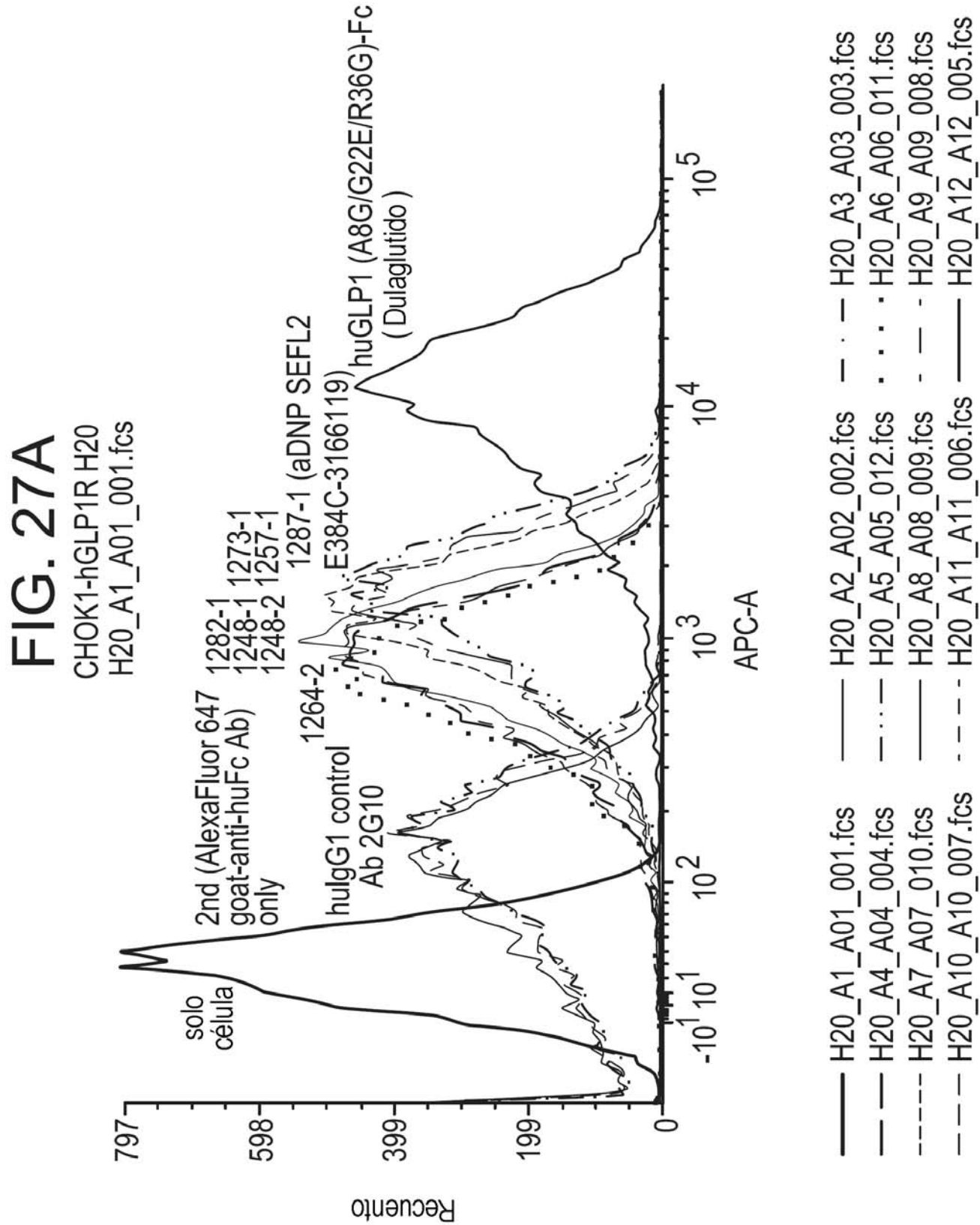


FIG. 27B

clon 10 de 293T-GIPR

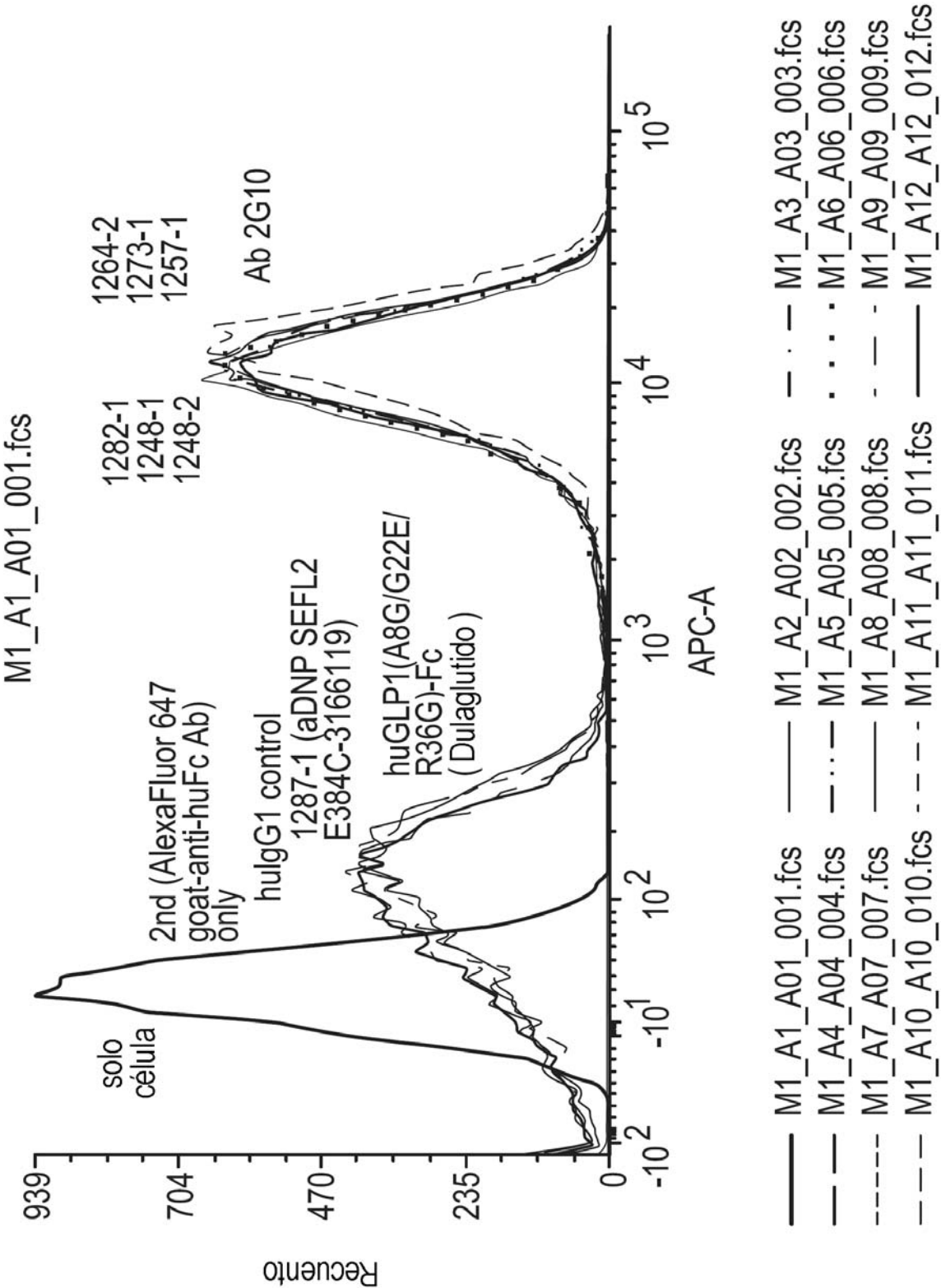
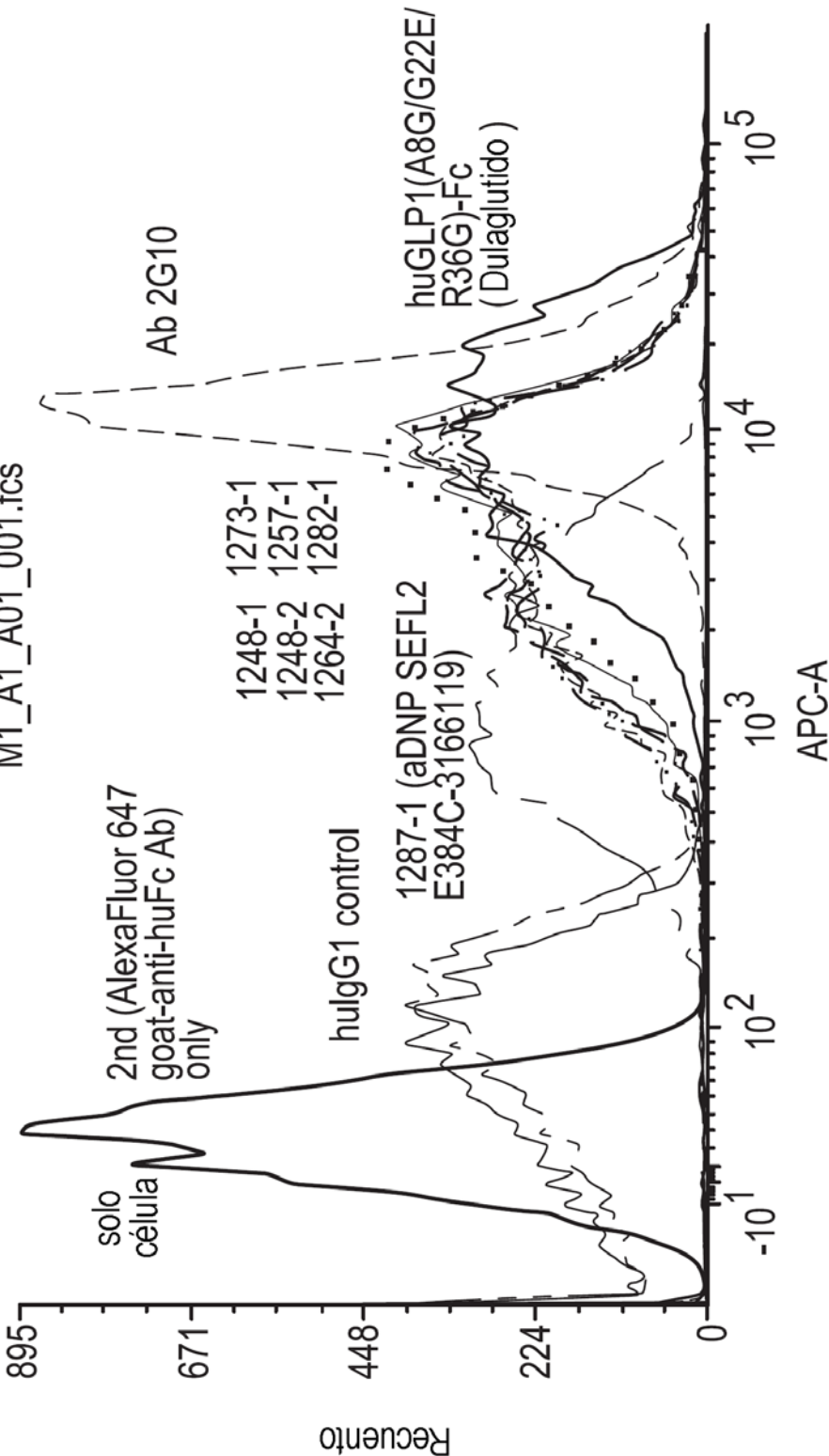


FIG. 27C

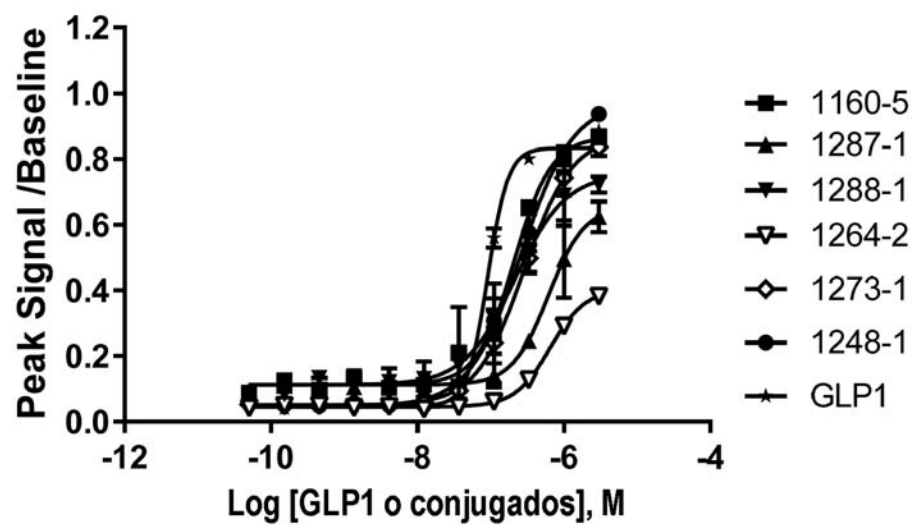
CHOK1-hGLP1R/hGIPR M1
M1_A1_A01_001.fcs



- M1_A1_A01_001.fcs — M1_A2_A02_002.fcs - - - M1_A3_A03_003.fcs
- - M1_A4_A04_004.fcs - - - M1_A5_A05_005.fcs . . . M1_A6_A06_006.fcs
- - - M1_A7_A07_007.fcs — M1_A8_A08_008.fcs - - - M1_A9_A09_009.fcs
- - - M1_A10_A10_010.fcs - - - M1_A11_A11_011.fcs — M1_A12_A12_012.fcs

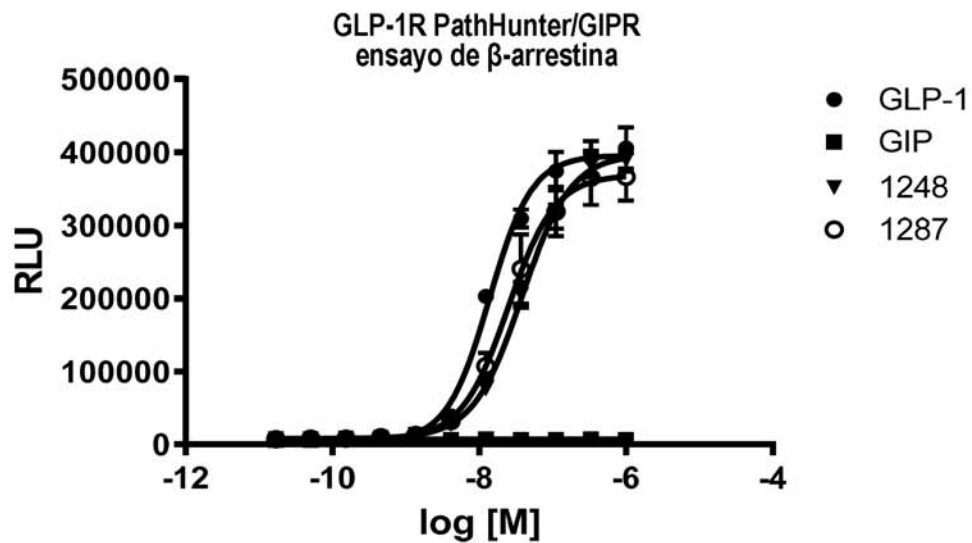
FIG. 28

Ensayo de flujo de calcio en células ChoK1 GLP1R/GIPR M1



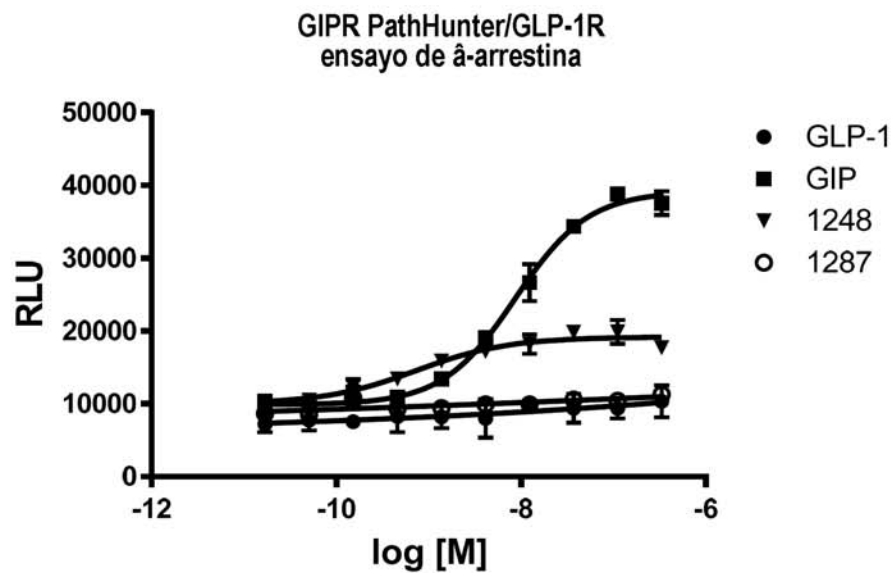
	1160-5	1287-1	1288-1	1264-2	1273-1	1248-1	GLP1
CE50	2.098e-007	6.152e-007	2.141e-007	6.485e-007	2.862e-007	2.594e-007	9.123e-008

FIG. 29A



	GIP	GLP-1	1248	1287
EC50	1.974e-010	1.379e-008	3.83e-008	2.493e-008

FIG. 29B



	GLP-1	GIP	1248	1287
EC50	1.689e+017	8.702e-009	7.363e-010	~ 4.234e-006

FIG. 30

Ensayo de secreción de insulina estimulada por glucosa:
condiciones de glucosa baja y elevada en microislotes
pancreáticos humanos

