June 16, 2026

Patent Owner Neurelis, Inc.

Hearing Demonstratives

IPR2025-00464, IPR2025-00465, IPR2025-00466

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Agenda

- No Collateral Estoppel
- Priority Date of '414 and '786 Patents
- Claim Construction
- Non-Obviousness
  - Failure to Disclose All Limitations
  - No Motivation to Combine
- Priority Date of Gwozdz-PCT
- Cartt-'784
- Petitioner's Motion to Strike
- Patent Owner's Motion to Strike
- Patent Owner's Motion to Exclude

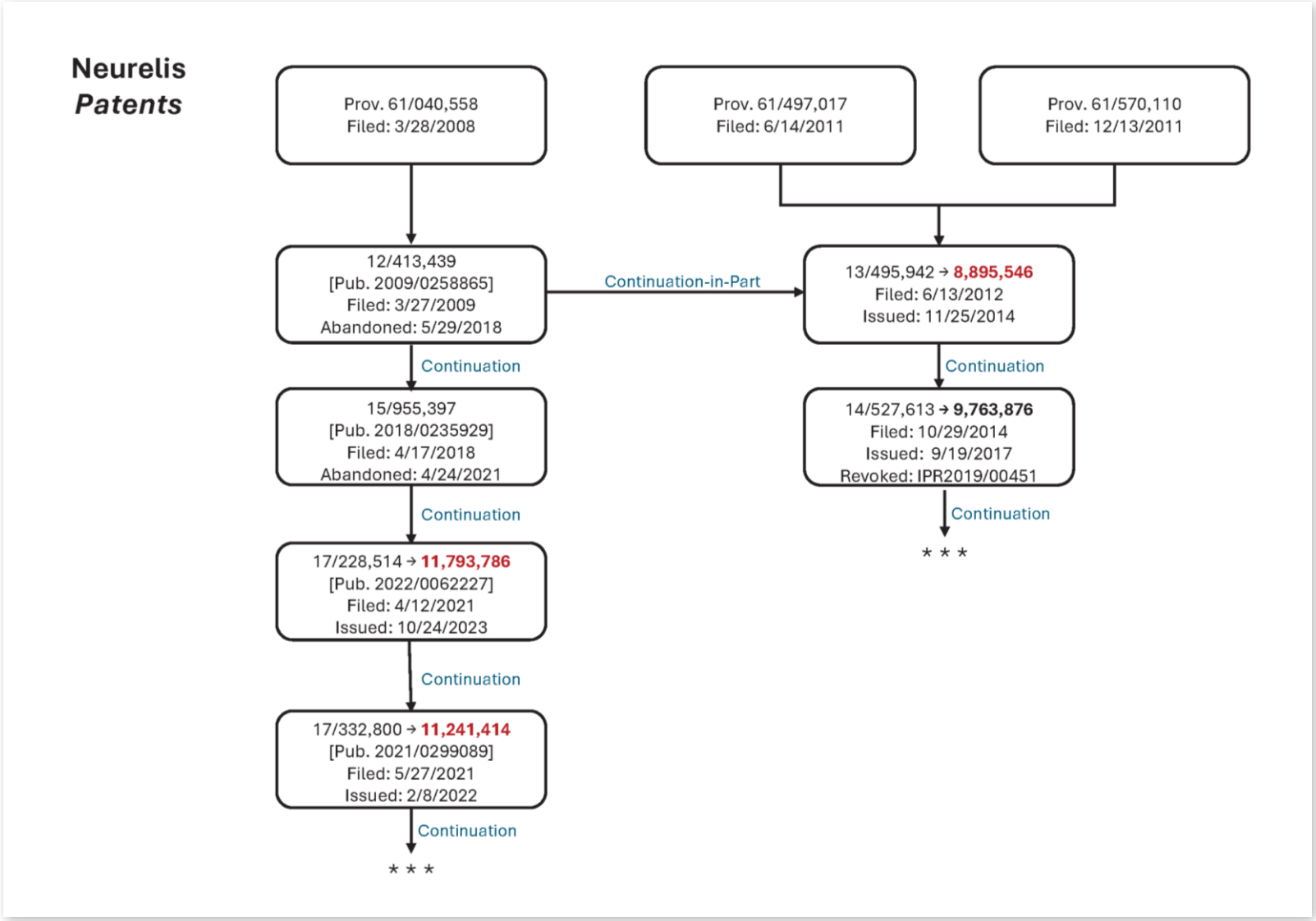
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Agenda

- No Collateral Estoppel
- Priority Date of '414 and '786 Patents
- Claim Construction
- Non-Obviousness
  - Failure to Disclose All Limitations
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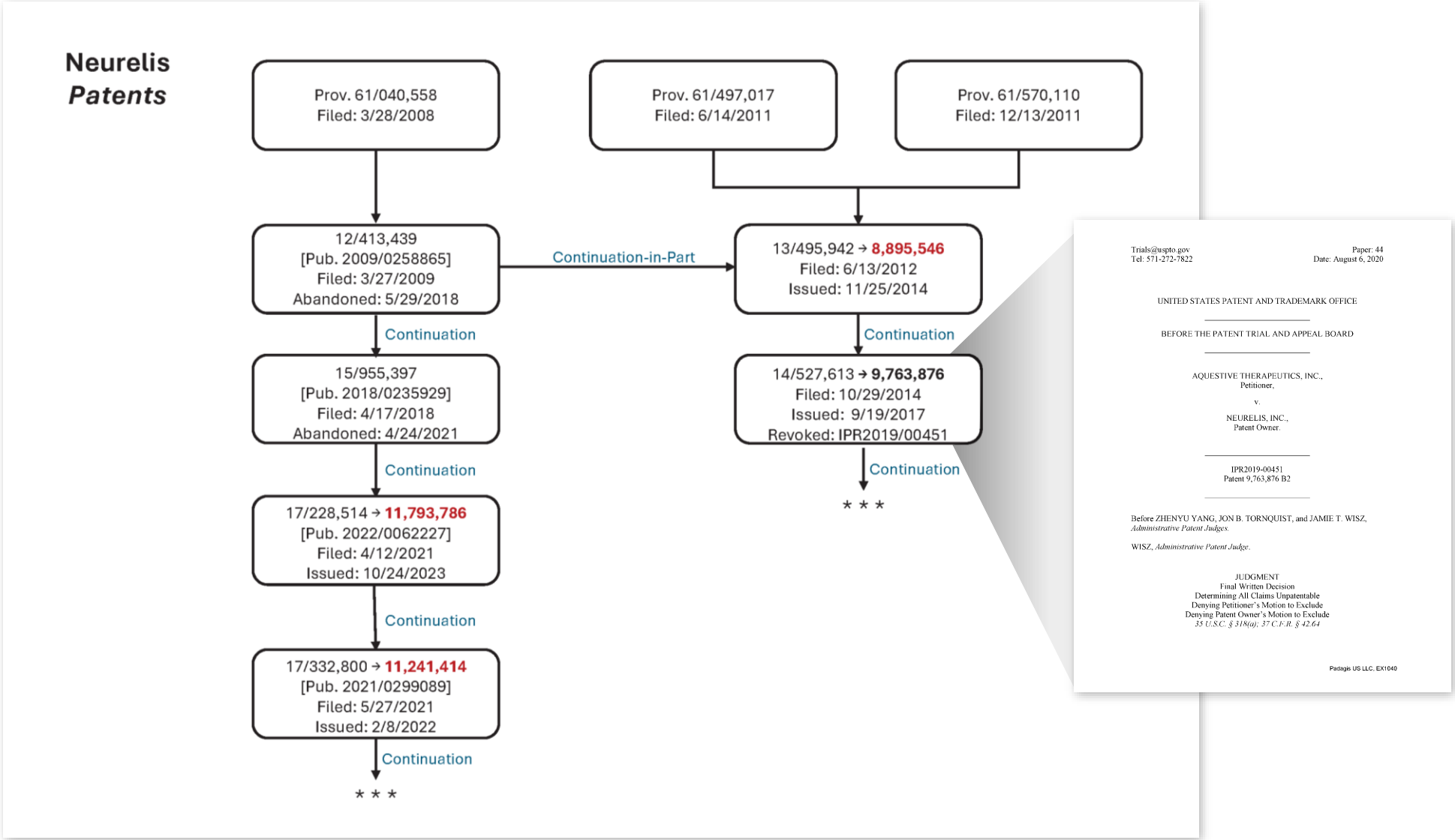
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Family Tree



DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Family Tree



Trials@uspto.gov
Tel: 571-272-7822

Paper: 44
Date: August 6, 2020

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AQUESTIVE THERAPEUTICS, INC.,
Petitioner,

v.

NEURELIS, INC.,
Patent Owner.

IPR2019-00451
Patent 9,763,876 B2

Before ZHENYU YANG, JON B. TORNQUIST, and JAMIE T. WISZ,
Administrative Patent Judges.

WISZ, *Administrative Patent Judge.*

JUDGMENT
Final Written Decision
Determining All Claims Unpatentable
Denying Petitioner's Motion to Exclude
Denying Patent Owner's Motion to Exclude
35 U.S.C. § 318(a); 37 C.F.R. § 42.64

Padagis US LLC, EX1040

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Requirements for Collateral Estoppel

"The party seeking to invoke collateral estoppel must show:

(1) the issue is identical to one decided in the first action;

(2) the issue was actually litigated in the first action;

(3) resolution of the issue was essential to a final judgment in the first action; and

(4) [the party against whom collateral estoppel is being asserted] had a full and fair opportunity to litigate the issue in the first action."

Google v. Hammond Development Int'l, Inc., 54 F.4th 1377, 1381 (Fed. Cir. 2022)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Material Differences

"[S]eparate patents describe separate and distinct inventions, and it cannot be presumed that related patents rise and fall together."

Comair Rotron, Inc. v. Nippon Densan Corp., 49 F.3d 1535, 1539 (Fed. Cir. 1995)

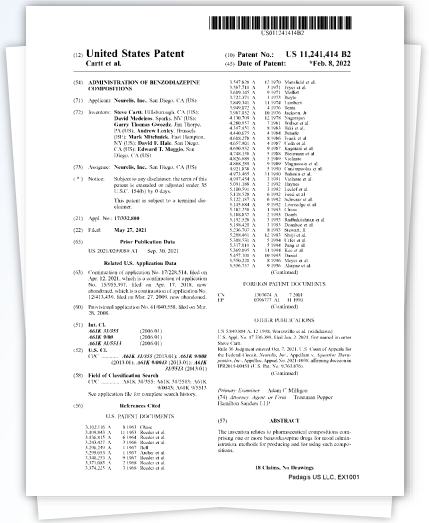
"[T]the district court correctly identified the dispositive issue as being 'whether the claims [in this 2014 Action] are materially different from those in [the previous action].'"

ParkerVision, Inc. v. Qualcomm Inc., 116 F.4th 1345, 1356 (Fed. Cir. 2024)

IPR2025-00465, Paper 28 (POR) at 65, 66

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

'414 Patent Claim 1



(12) **United States Patent**
Carli et al.

(10) **Patent No.: US 11,241,414 B2**
(45) **Date of Patent: *Feb. 8, 2022**

(54) **ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS**

(71) Applicant: **Neurelis, Inc.**, San Diego, CA (US)

(72) Inventors: **Steve Carli**, Hillsborough, CA (US); **David Madden**, Arpaka, PA (US); **Garry Thomas Cowsill**, Jan Thorpe, PA (US); **Andrew Lesley**, Brussels (BE); **Mark Michalski**, Fort Thompson, NY (US); **David E. Hale**, San Diego, CA (US); **Edward T. Maggio**, San Diego, CA (US)

(73) Assignee: **Neurelis, Inc.**, San Diego, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **17/352,880**

(22) Filed: **May 27, 2021**

(65) **Prior Publication Data**

US 2021/0290604 A1 Sep. 30, 2021

Related U.S. Application Data

(63) Continuation of application No. 17/229,514, filed on Apr. 12, 2021, which is a continuation of application No. 16/953,597, filed on Apr. 17, 2018, now abandoned, which is a continuation of application No. 12/413,450, filed on Mar. 27, 2009, now abandoned.

(60) Provisional application No. 61/040,558, filed on Mar. 28, 2008.

(51) **Int. Cl.**
A61K 47/44 (2006.01)
A61K 9/00 (2006.01)
A61K 31/5513 (2006.01)

(52) **U.S. Cl.**
CPC **A61K 31/553** (2013.01); **A61K 9/008** (2013.01); **A61K 9/0012** (2013.01); **A61K 31/5513** (2013.01)

(58) **Field of Classification Search**
CPC A61K 31/553; A61K 31/5513; A61K 9/0019; A61K 9/0012; A61K 9/008
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,332,110 A 7/1967 Chien
3,839,845 A 11/1974 Bender et al.
3,920,837 A 11/1975 Bender et al.
3,936,455 A 2/1976 Bell
3,996,195 A 12/1976 Sato et al.
4,138,478 A 2/1979 Nagarsenker
4,280,957 A 7/1981 Bolhuis et al.
4,327,725 A 5/1982 Cortese et al.
4,440,675 A 4/1984 Bender
4,610,870 A 9/1986 Frank et al.
4,615,697 A 10/1986 Robinson
4,690,932 A 9/1987 Kaplan et al.
4,740,358 A 4/1988 Herrmann et al.
4,826,689 A 5/1989 Vickers
4,880,298 A 11/1989 Magnusson et al.
4,894,235 A 1/1990 Mezei et al.
4,975,469 A 12/1990 Nelson et al.
4,997,454 A 3/1991 Vickers et al.
5,011,915 A 4/1991 Sato et al.
5,180,594 A 1/1993 Liedtke et al.
5,412,128 A 4/1995 Imai et al.
5,147,643 A 9/1992 Schroeder et al.
5,149,842 A 9/1992 Liversidge et al.
5,182,378 A 1/1993 Chen
5,190,975 A 3/1993 Dumitr
5,192,528 A 3/1993 Radebaugh et al.
5,208,257 A 5/1993 Bender et al.
5,236,707 A 8/1993 Bender, II
5,280,491 A 12/1993 Mezei et al.
5,296,222 A 3/1994 Wong et al.
5,317,161 A 5/1994 Dong et al.
5,349,001 A 11/1994 Kao et al.
5,376,645 A 12/1994 Kao
5,390,228 A 2/1995 Mezei et al.
5,506,215 A 9/1996 Harwood et al.
(Continued)

FOREIGN PATENT DOCUMENTS

CN 1830474 A 7/2001
EP 0594777 A1 11/1993
(Continued)

OTHER PUBLICATIONS

US 5,643,604 A, 12/1998, Nazzolillo et al. (withdrawn)
U.S. Appl. No. 61/746,399, filed Jan. 2, 2013. Not named in earlier Statement.
Rule 36 Judgment entered Oct. 7, 2021, U.S. Court of Appeals for the Federal Circuit, Neurelis, Inc., Appellant v. Aquestive Therapeutics Inc., Appellee, Appeal No. 2021-1939, affirming decision in IPR2019-00419 of U.S. Pat. No. 9,763,926.
(Continued)

Primary Examiner Adam C Milligan
(74) *Attorney, Agent, or Firm* Troutman Pepper Hamilton Sanders LLP

(57) **ABSTRACT**

The inventors relate to pharmaceutical compositions comprising one or more benzodiazepine drugs for rectal administration, methods for producing and for using such compositions.

18 Claims, No Drawings

Page 1 of 15

Paragis US LLC, EX1001

'414 Patent

What is claimed is:

1. A pharmaceutical solution for nasal administration consisting of:

diazepam or a pharmaceutically acceptable salt thereof;

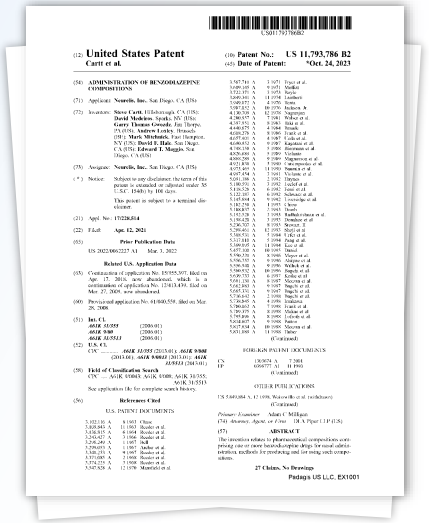
one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from 30% to 95% (w/w);

ethanol and benzyl alcohol in a combined amount from 10% to 70% (w/w); and

n-dodecyl beta-D-maltoside.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

'786 Patent Claim 1



'786 Patent

What is claimed is:

1. A pharmaceutical solution for nasal administration consisting of:

a therapeutically effective amount of diazepam or a pharmaceutically acceptable salt thereof;

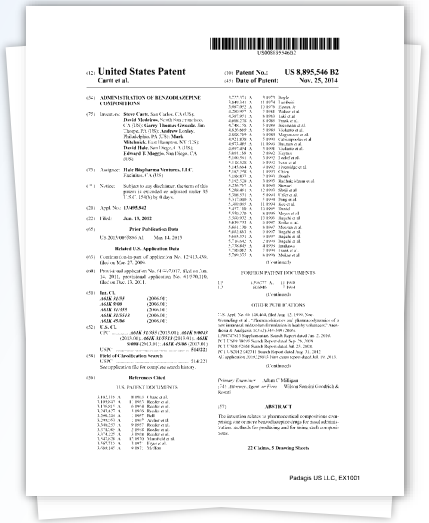
one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any isomers thereof, any esters thereof, and any combinations thereof, in an amount from 30% to 95% (w/w);

one or more alcohols in an amount from 10% to 70% (w/w), wherein the one or more alcohols comprises benzyl alcohol; and

n-dodecyl beta-D-maltoside.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

'546 Patent Claims 17 and 22



'546 Patent

What is claimed is:

1. A pharmaceutical solution for nasal administration consisting of:

(a) a benzodiazepine drug;

(b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w);

(c) ethanol and benzyl alcohol in a combined amount from about 10% to about 70% (w/w); and

(d) an alkyl glycoside.

15. The pharmaceutical solution of claim 1, wherein the alkyl glycoside is present in pharmaceutical solution in a concentration of at least about 0.01% (w/w).

16. The pharmaceutical solution of claim 15, wherein the alkyl glycoside is present in the pharmaceutical solution in an amount of 0.01% to 1% (w/w).

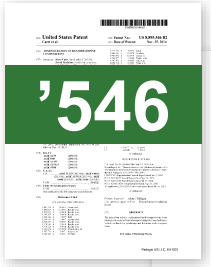
17. The solution of claim 1, consisting of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.

22. The solution of claim 16, wherein the alkyl glycoside is dodecyl maltoside.

IPR2025-00464, EX1001 at cl. 1-22

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

'546 Patent Claims 17 and 22



What is claimed is:

1. A pharmaceutical solution for nasal administration consisting of:

(a) a benzodiazepine drug;

(b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w);

(c) ethanol and benzyl alcohol in a combined amount from about 10% to about 70% (w/w); and

(d) an alkyl glycoside.

15. The pharmaceutical solution of claim 1, wherein the alkyl glycoside is present in pharmaceutical solution in a concentration of at least about 0.01% (w/w).

16. The pharmaceutical solution of claim 15, wherein the alkyl glycoside is present in the pharmaceutical solution in an amount of 0.01% to 1% (w/w).

17. The solution of claim 1, consisting of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.

22. The solution of claim 16, wherein the alkyl glycoside is dodecyl maltoside.



Statutory Disclaimer (EX2075)

DISCLAIMER IN A PATENT UNDER 37 CFR 1.321(a)

Name of Patentee: Neurelis, Inc.	Docket Number (optional): 148570-004321
Patent Number: 8,895,546	Date Patent Issued: November 25, 2014
Title of Invention: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

Patentee hereby disclaims:

☑ the following complete claim(s) in the above-identified patent: 1-16, 18-21.

IPR2025-00464, Paper 28 (POR) at 4, EX1001 at cl. 1-22

Comparison of Independent Claims

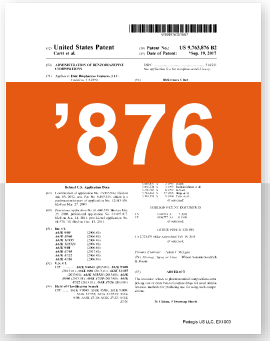
9,763,876	11,241,414	11,793,786	8,895,546
1. A method of treating a patient with a disorder which is treatable with a benzodiazepine drug, comprising: administering to one or more nasal mucosal membranes of a patient a pharmaceutical solution for nasal administration consisting of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); ethanol and benzyl alcohol in a combined amount from about 10% to about 70% (w/w); and an alkyl glycoside.	1. A pharmaceutical solution for nasal administration consisting of: diazepam or a pharmaceutically acceptable salt thereof; one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from 30% to 95% (w/w); ethanol and benzyl alcohol in a combined amount from 10% to 70% (w/w); and n-dodecyl beta-D-maltoside.	1. A pharmaceutical solution for nasal administration consisting of: a therapeutically effective amount of diazepam or a pharmaceutically acceptable salt thereof; one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ- tocotrienol, δ-tocotrienol, tocophersolan, any isomers thereof, any esters thereof, and any combinations thereof, in an amount from 30% to 95% (w/w); one or more alcohols in an amount from 10% to 70% (w/w), wherein the one or more alcohols comprises benzyl alcohol; and n-dodecyl beta-D-maltoside	1. A pharmaceutical solution for nasal administration consisting of: (a) a benzodiazepine drug; (b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); (c) ethanol and benzyl alcohol in a combined amount from about 10% to about 70% (w/w); and (d) an alkyl glycoside. 17. The solution of claim 1, consisting of diazepam, Vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Collateral Estoppel Does Not Apply: Priority Date

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Priority Date: Materially Different Issues

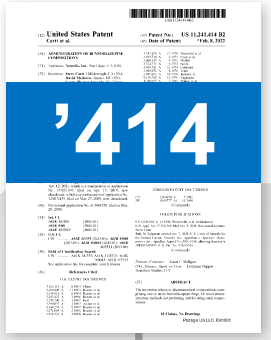


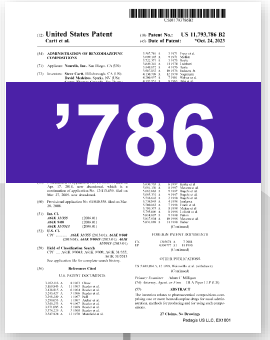
alkyl glycoside

Independent

dodecyl maltoside

Dependent





n-dodecyl beta-D-maltoside

Independent

"[E]ach case involving the issue of written description must be decided on its own facts."

Amgen Inc. v. Sanofi, 872 F.3d 1367, 1377 (Fed. Cir. 2017)

"Whether a species is described adequately under 35 U.S.C. §112 versus whether a class/genera inclusive of the species is described are not identical inquiries."

IPR2025-00465, Paper 13 (Inst. Dec.) at 22

IPR2025-00465, Paper 28 (POR) at 68–69

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Priority Date: Dependent Claims Not Actually Litigated

- "Claim 1 requires 'an alkyl glycoside.' … Since all of the remaining claims of the '876 patent depend, directly or indirectly, from Claim 1, they also require the presence of 'an alkyl glycoside.'"

EX1040 (-451 FWD) at 14 n.6

- "[T]he '558 provisional does not provide adequate written description support for the 'alkyl glycoside' limitation. Therefore, the claims of the '876 patent are not entitled to the benefit of priority to the '558 provisional."

EX1040 (-451 FWD) at 23

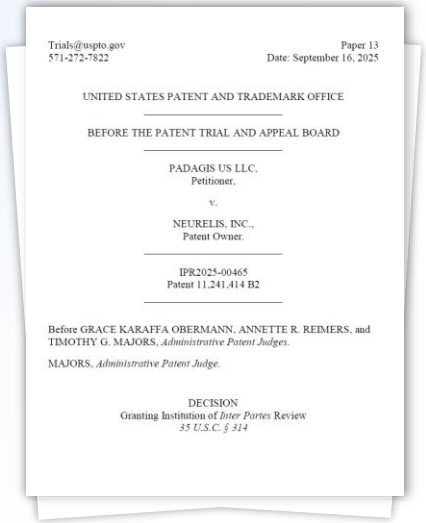
- "[A] POSA would have recognized and understood that alkyl glycosides were disclosed and supported…."

EX2076 (-451 POR) at 24

IPR2025-00465, Paper 28 (POR) at 68–70

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Priority Date: Dependent Claims Not Actually Litigated



Trials@uspto.gov
571-272-7822

Paper 13
Date: September 16, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PADAGIS US LLC,
Petitioner,

v.

NEURELIS, INC.,
Patent Owner.

IPR2025-00465
Patent 11,241,414 B2

Before GRACE KARAFFA OBERMANN, ANNETTE R. REIMERS, and TIMOTHY G. MAJORS, *Administrative Patent Judges*.

MAJORS, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

Institution Decision IPR2025-00465

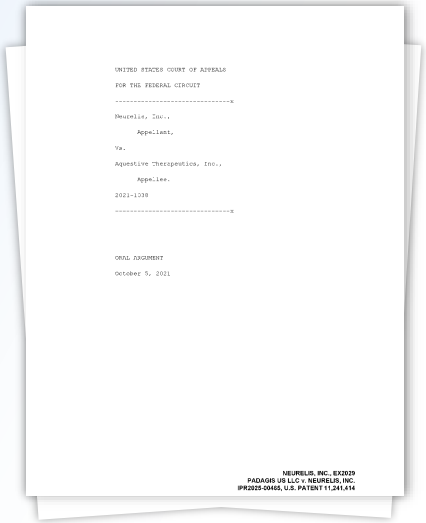
The record is ambiguous in showing that, during the 451 IPR, the parties joined issue and actually litigated the sufficiency of written description support for those dependent claims reciting dodecyl maltoside. *First*, in the 451 IPR trial proceedings, Patent Owner's only separate suggestion of adequate written description for the subject dependent claims appears to have been relegated to a footnote. *See* Ex. 2029, 2 (Chief Judge Moore of the Federal Circuit asking about waiver and suggesting Patent Owner's position before the Board on the dependent claims "was made only in a single footnote in passing and [was] not a developed argument"); IPR2019-00451, Paper 16 (Patent Owner Response) at 19 n.7.

IPR2025-00465, Paper 13 (Inst. Dec.) at 23

IPR2025-00465, Paper 28 (POR) at 68–70

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Priority Date: Dependent Claims Not Actually Litigated


UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

Neurelis, Inc.,
Appellant,
Vs.
Aquestive Therapeutics, Inc.,
Appellee.
2021-1038

ORAL ARGUMENT
October 5, 2021
NEURELIS, INC., EX2029
PADAGIS US LLC v. NEURELIS, INC.
IPR2025-00465, U.S. PATENT 11,241,414

EX2029

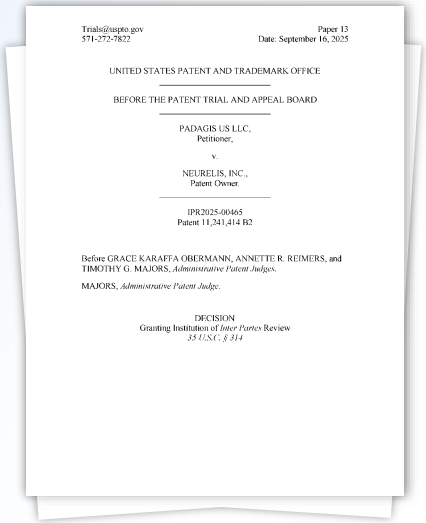
CHIEF JUDGE MOORE: Before you go into the merits, would you just address the waiver argument? Because I understand your opponent to suggest that you didn't make this argument below. It was made only in a single footnote in passing and not a developed argument. So can you show us where you made this argument below in a way that alerted the Board to the fact that you were separately arguing dependent claims and not just hinging your argument on a representative claim, as lawyers often do in these cases?

EX2029 at 3

IPR2025-00465, Paper 28 (POR) at 70, Paper 53 (Sur-Reply) at 6

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Priority Date: Dependent Claims Not Actually Litigated



Trials@uspto.gov
571-272-7822

Paper 13
Date: September 16, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PADAGIS US LLC,
Petitioner,

v.

NEURELIS, INC.,
Patent Owner.

IPR2025-00465
Patent 11,241,414 B2

Before GRACE KARAFFA OBERMANN, ANNETTE R. REIMERS, and TIMOTHY G. MAJORS, *Administrative Patent Judges*.

MAJORS, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

Institution Decision
Paper 13

[13] As the Federal Circuit explains, collateral estoppel does not apply to issues that might have been but were not actually litigated and determined in a prior action. *Purdue Pharma L.P. v. Iancu*, 767 F. App'x 918, 922 (Fed. Cir. 2019) (citing the Restatement (Second) of Judgments for the proposition that issues are "not actually litigated" if, for example, they not denied in a responsive pleading, or if based on stipulations, consent, or default); Restatement (Second) of Judgments § 27, cmt. e. (Am. Law. Inst. 1982).

IPR2025-00465, Paper 13 (Inst. Dec.) at 24 n.13

IPR2025-00465, Paper 28 (POR) at 69-70, Paper 53 (Sur-Reply) at 4

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Priority Date: Dependent Claims Not Actually Litigated

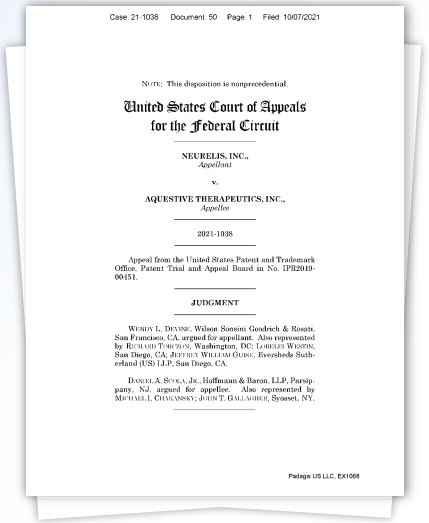
"The Board based its collateral estoppel ruling on the notion that collateral estoppel applies to issues that were or ***could have been raised*** in the prior litigation."

"An issue is not actually litigated if…it is raised by a material allegation of a party's pleading but is admitted (explicitly or by virtue of a failure to deny) in a responsive pleading [or] if it is a stipulation between the parties."

Purdue Pharma L.P. v. Iancu, 767 Fed. Appx. 918, 922-923 (Fed. Cir. 2019) (internal quotations removed)

IPR2025-00465, Paper 28 (POR) at 69-70, Paper 53 (Sur-Reply) at 4

Rule 36 Affirmance



Case: 21-1038 Document: 50 Page: 1 Filed: 10/07/2021

NOTE: This disposition is nonprecedential.

United States Court of Appeals
for the Federal Circuit

NEURELIS, INC.,
Appellant

v.

AQUESTIVE THERAPEUTICS, INC.,
Appellee

2021-1038

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2019-00151.

JUDGMENT

WENDY L. DEVINE, Wilson Sonsini Goodrich & Rosati, San Francisco, CA, argued for appellant. Also represented by RICHARD TORCZON, Washington, DC; LORELEI WESTIN, San Diego, CA; JEFFREY WILLIAM GUISE, Eversheds Sutherland (US) LLP, San Diego, CA.

DANIEL A. SCOLA, JR., Hoffmann & Baron, LLP, Parsippany, NJ, argued for appellee. Also represented by MICHAEL L. CHAKANSKY; JOHN T. GALLAGHER, Syosset, NY.

Padagis US LLC, EX1068

EX1068

PER CURIAM (MOORE, *Chief Judge*, NEWMAN and REYNA, *Circuit Judges*).

AFFIRMED. See Fed. Cir. R. 36.

ENTERED BY ORDER OF THE COURT

October 7, 2021
Date

/s/ Peter R. Marksteiner
Peter R. Marksteiner
Clerk of Court

EX1068 at 2

"The party seeking to invoke collateral estoppel must show: …

(3) resolution of the issue was essential to a final judgment in the first action"

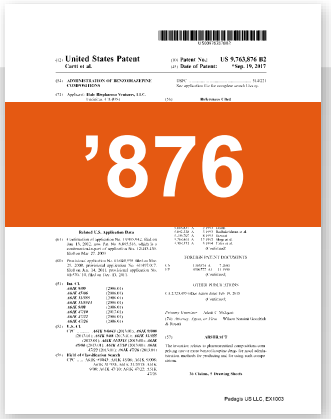
Google v. Hammond Development Int'l, Inc., 54 F.4th 1377, 1381 (Fed. Cir. 2022)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Collateral Estoppel Does Not Apply: Obviousness

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Obviousness: Motivation to Combine

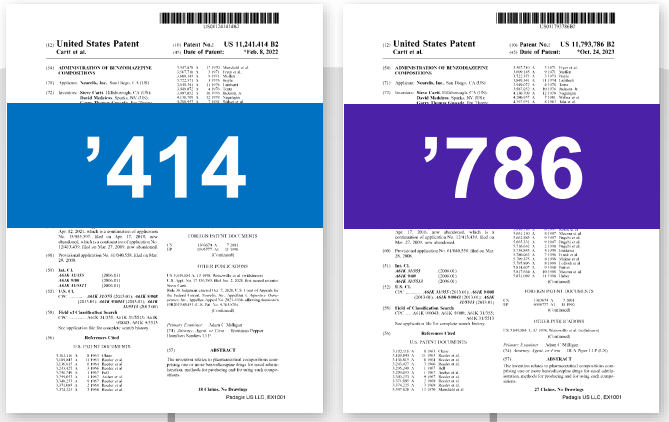


alkyl glycoside

Independent

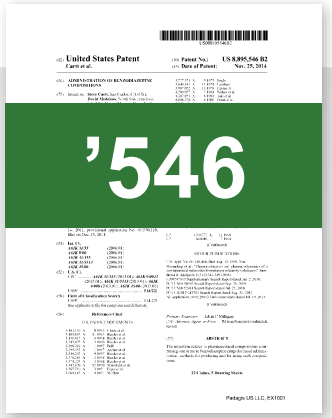
dodecyl maltoside

Dependent



n-dodecyl beta-D-maltoside

Independent

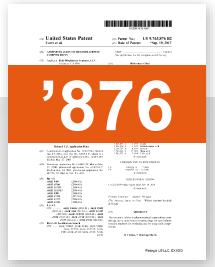


dodecyl maltoside

Independent

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Obviousness: Materially Different Issues

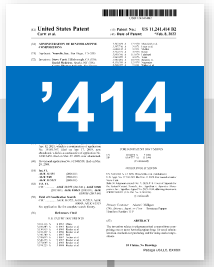


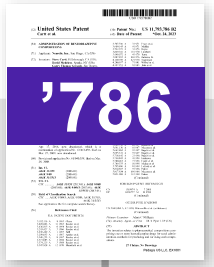
alkyl glycoside

Independent

dodecyl maltoside

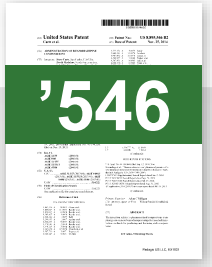
Dependent





n-dodecyl beta-D-maltoside

Independent



dodecyl maltoside

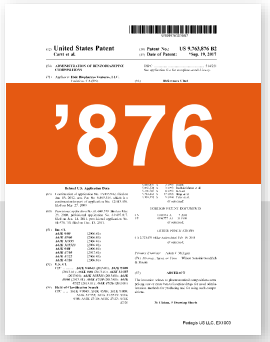
Independent

"Obviousness concerns whether a skilled artisan ***not only could have*** made ***but would have*** been motivated to make the combinations or modifications of prior art ***to arrive at the claimed invention***."

Virtek Vision Int'l ULC v. Assembly Guidance Sys., Inc., 97 F.4th 882 (Fed. Cir. 2024) (quoting *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015))

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Obviousness: Materially Different Issues

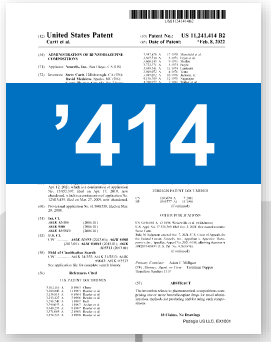


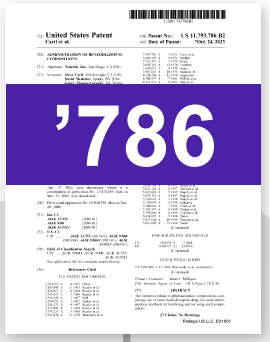
alkyl glycoside

Independent

dodecyl maltoside

Dependent





n-dodecyl beta-D-maltoside

Independent

"We first must determine whether [challenger] carried its burden to ***prove that all claimed limitations are disclosed in the prior art***. … [C]onsider motivation to combine and reasonable expectation of success only 'if all the elements of an invention are found in a combination of prior art references."

PAR Pharm., Inc. v. TWI Pharms., Inc., 773 F.3d 1186, 1194 (Fed. Cir. 2014) (internal citations omitted)

IPR2025-00465, Paper 28 (POR) at 3, 39

Obviousness of *n*-dodecyl β-D-maltoside or DDM

"[D]isclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus."

Atofina v. Great Lakes Chem. Corp., 441 F.3d 991, 999 (Fed. Cir. 2006)

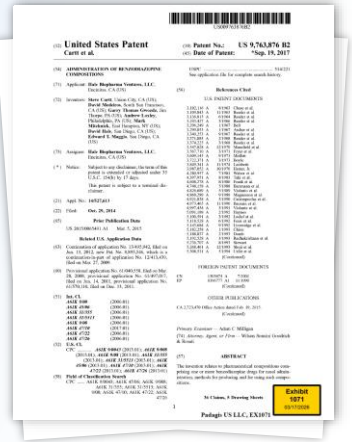
"The Board based its collateral estoppel ruling on the notion that collateral estoppel applies to issues that were or ***could have been raised*** in the prior litigation."

"An issue is not actually litigated if … it is raised by a material allegation of a party's pleading but is admitted (explicitly or by virtue of a failure to deny) in a responsive pleading [or] if it is a stipulation between the parties."

Purdue Pharma L.P. v. Iancu, 767 Fed. Appx. 918, 922-923 (Fed. Cir. 2019) (internal quotations removed)

IPR2025-00465, Paper 28 (POR) at 69-70, Paper 53 (Sur-Reply) at 3, 4

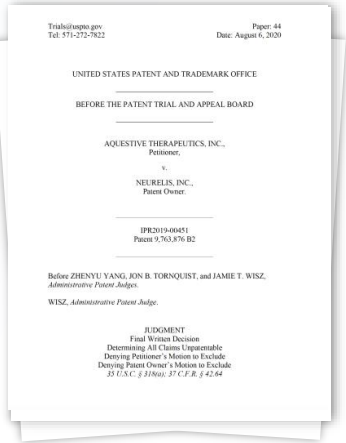
Obviousness of *n*-dodecyl β-D-maltoside or dodecyl maltoside



9,763,876
EX1071

1. A method of treating a patient with a disorder which is treatable with a benzodiazepine drug, comprising: administering to one or more nasal mucosal membranes of a patient a pharmaceutical solution for nasal administration consisting of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); ethanol and benzyl alcohol in a combined amount from about 10% to about 70% (w/w); and an alkyl glycoside.

25. The method of claim 24, wherein the solution contains about 0.01% to 1% (w/w) of an alkyl glycoside.
26. The method of claim 25, wherein the solution contains about 0.01% to 1% (w/w) of dodecyl maltoside.
27. The method of claim 1, wherein the solution consists of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.
28. The method of claim 1, wherein the solution consists of about 56.47% (w/v) vitamin E, about 10.5% (w/v) benzyl alcohol, about 10% (w/v) diazepam, about 0.25%(w/v) dodecyl maltoside, q.s. dehydrated ethanol.



451 FWD
EX1040

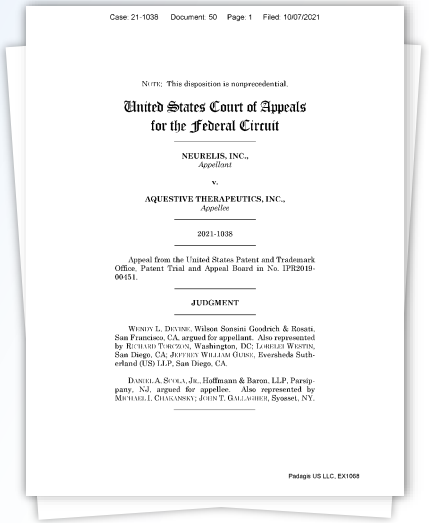
Patent Owner does not present separate arguments for any of the dependent claims. *See generally* PO Resp. 23–38.

EX1040 at 27

IPR2025-00465, Paper 53 (Sur-Reply) at 4-5

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Rule 36 Affirmance


Case: 21-1038 Document: 50 Page: 1 Filed: 10/07/2021

NOTE: This disposition is nonprecedential.

United States Court of Appeals
for the Federal Circuit

NEURELIS, INC.,
Appellant

v.

AQUESTIVE THERAPEUTICS, INC.,
Appellee

2021-1038

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2019-00151.

JUDGMENT

WENDY L. DEVINE, Wilson Sonsini Goodrich & Rosati, San Francisco, CA, argued for appellant. Also represented by RICHARD TORCZON, Washington, DC; LORELEI WESTIN, San Diego, CA; JEFFREY WILLIAM GUISE, Eversheds Sutherland (US) LLP, San Diego, CA.

DANIEL A. SCOLA, JR., Hoffmann & Baron, LLP, Parsippany, NJ, argued for appellee. Also represented by MICHAEL L. CHAKANSKY; JOHN T. GALLAGHER, Syosset, NY.

Padagis US LLC, EX1068

EX1068

PER CURIAM (MOORE, *Chief Judge*, NEWMAN and REYNA, *Circuit Judges*).

AFFIRMED. See Fed. Cir. R. 36.

ENTERED BY ORDER OF THE COURT

October 7, 2021
Date

/s/ Peter R. Marksteiner
Peter R. Marksteiner
Clerk of Court

EX1068 at 2

"The party seeking to invoke collateral estoppel must show: …

(3) resolution of the issue was essential to a final judgment in the first action"

Google v. Hammond Development Int'l, Inc., 54 F.4th 1377, 1381 (Fed. Cir. 2022)

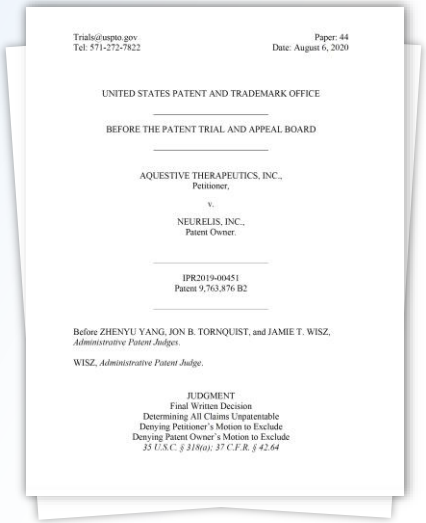
IPR2025-00465, Paper 28 (POR) at 70, Paper 53 (Sur-Reply) at 6

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Collateral Estoppel Does Not Apply: Priority Date of Gwozdz-PCT

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Gwozdz-PCT Priority Date: Not Actually Litigated



Trials@uspto.gov
Tel: 571-272-7822

Paper: 44
Date: August 6, 2020

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AQUESTIVE THERAPEUTICS, INC.,
Petitioner,

v.

NEURELIS, INC.,
Patent Owner.

IPR2019-00451
Patent 9,763,876 B2

Before ZHENYU YANG, JON B. TORNQUIST, and JAMIE T. WISZ,
Administrative Patent Judges.

WISZ, *Administrative Patent Judge.*

JUDGMENT
Final Written Decision
Determining All Claims Unpatentable
Denying Petitioner's Motion to Exclude
Denying Patent Owner's Motion to Exclude
35 U.S.C. § 318(a); 37 C.F.R. § 42.64

-451 FWD
EX1040

provisional") (Ex. 1046). *Id.* at 6. Petitioner has shown that the claims of Gwozdz are supported by the Gwozdz provisional, "at least because Gwozdz's claims are literally identical to the claims filed in [the] Gwozdz provisional." *Id.* (citing Ex. 1014, 14–15; Ex. 1046, 19–20); *see* Ex. 1014, 4–10; Ex. 1046, 9–15. Patent Owner does not contest that Gwozdz is entitled to this filing date. *See* PO Resp. 17–23. Therefore, we find that

EX1040 at 14

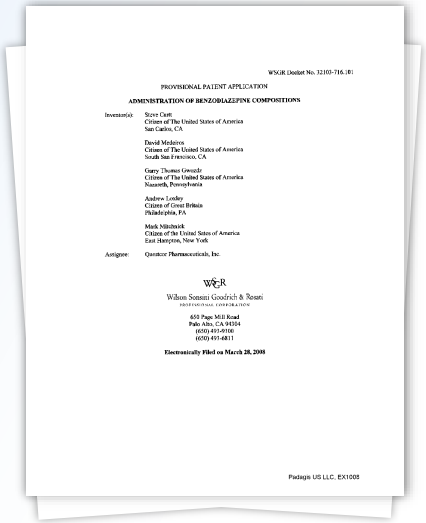
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Agenda

- No Collateral Estoppel
- Priority Date of '414 and '786 Patents
- Claim Construction
- Non-Obviousness
  - Failure to Disclose All Limitations
  - No Motivation to Combine
- Priority Date of Gwozdz-PCT
- Cartt-'784
- Petitioner's Motion to Strike
- Patent Owner's Motion to Strike
- Patent Owner's Motion to Exclude

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

'558 Provisional



WSGR Docket No. 32103-716.101

PROVISIONAL PATENT APPLICATION

ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

Inventor(s): Steve Cutt
Citizen of The United States of America
San Carlos, CA

David Medaiva
Citizen of The United States of America
South San Francisco, CA

Garry Thomas Gwozdz
Citizen of The United States of America
Nazareth, Pennsylvania

Andrew Lesley
Citizen of Great Britain
Philadelphia, PA

Mark Milshtein
Citizen of the United States of America
East Hampton, New York

Assignee: Questcor Pharmaceuticals, Inc.

WSGR
Wilson Sonsini Goodrich & Rosati
PROFESSIONAL CORPORATION

650 Page Mill Road
Palo Alto, CA 94304
(650) 493-9300
(650) 493-6811

Electronically Filed on March 28, 2008

Pladaris US LLC, EX1008

'558 Provisional
EX1008

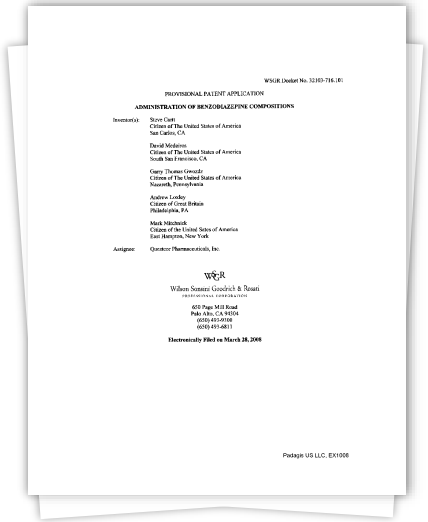
[152] In some embodiments, enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), acyl glycerols, fatty acids and salts, tyloxapol and biological detergents listed in the SIGMA Catalog, 1988, page 316-321 (which is incorporated herein by reference). Also agents that modify the membrane fluidity and permeability are appropriate such as enamines (e.g. phenylalanine enamine of ethylacetoacetate), malonates (e.g. diethyleneoxymethylene malonate), salicylates, bile salts and analogues and fusidates. Suitable concentrations are up to 20% w/v.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Requirements for Incorporation

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Requirements to Incorporate



PROVISIONAL PATENT APPLICATION

ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

Wilson Sonsini Goodrich & Rosati

Electronically Filed on March 28, 2008

Pedagio US LLC, EX1008

'558 Provisional
EX1008

[152] In some embodiments, enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), acyl glycerols, fatty acids and salts, tyloxapol and biological detergents listed in the SIGMA Catalog, 1988, page 316-321 (which is incorporated herein by reference). Also agents that modify the membrane fluidity and permeability are appropriate such as enamines (e.g. phenylalanine enamine of ethylacetoacetate), malonates (e.g. diethyleneoxymethylene malonate), salicylates, bile salts and analogues and fusidates. Suitable concentrations are up to 20% w/v.

"To incorporate matter by reference, a host document must contain language 'clearly identifying the subject matter which is incorporated and where it is to be found."

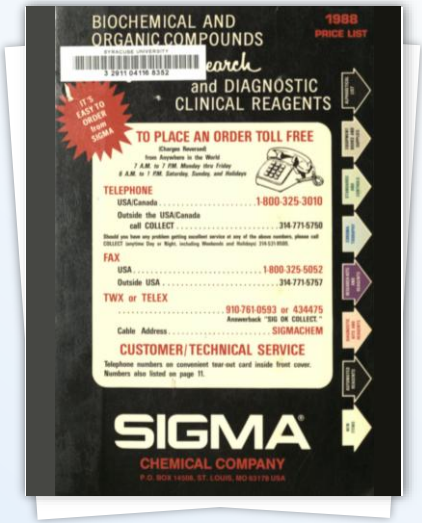
Callaway Golf Co. v. Acushnet Co., 576 F.3d 1331, 1346 (Fed. Cir. 2009)

IPR2025-00465, Paper 53 (Sur-Reply) at 7-8

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Sigma Catalog

Dr. Donovan



Sigma Catalog
EX1026

Q. I reckon you're familiar with the Sigma catalog from the context or research?

A. Back in the days when it was a catalog, yes.

Q. Could I ask you to turn to the second page of the document, page 2.

A. Okay.

Q. Do you see here a table of contents, correct?

A. Yes.

Q. This document that you have in your hand is an excerpt of a much larger book having at least 1800 pages, right?

A. Yes.

. . .

Q. Thank you. It's fair to say that back when the Sigma catalog was a physical object, it was widely distributed amongst researchers in the field, correct?

A. Yes.

EX2070 (Donovan Dep. Tr.) at 151:1–14; 179:8–12

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Provisional Is Not Essential

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Sigma Catalog and Provisional Are Not "Essential"

"[W]hether certain disclosure is 'essential' depends entirely on what the claims recite in the particular application, not the claims in the later-filed application."

Samsung Electrons. Co. v. Acqis LLC, IPR2021-00608, Paper 10 at 12 (P.T.A.B. Dec. 8, 2021)

"'Essential material' is material that is necessary to: (1) Provide a written description of ***the claimed invention***."

37 C.F.R. § 1.57(d)(1)

IPR2025-00465, Paper 28 (POR) at 23, Paper 53 (Sur-Reply) at 8

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Provisional Applications Need Not Include Claims



"**(b) Provisional Application.—**

. . .

(2) Claim.—
A claim, as required by subsections (b) through (e) of section 112, shall not be required in a provisional application."

35 U.S.C. § 111(b)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Provisional Is More Informal

"The Act [URAA] provides a mechanism to enable domestic applicants to quickly and inexpensively file provisional applications. Under the provisions of 35 U.S.C. 119(e), applicants are entitled to claim the benefit of priority in a given application in the United States."

M.P.E.P. § 201.04(III)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

M.P.E.P. § 608.01(p)

"***The limitations on the material which may be incorporated by reference in U.S. patent applications which are to issue as U.S. patents do not apply to applications relied on only to establish an earlier effective filing date under 35 U.S.C. 119 or 35 U.S.C. 120***. Neither 35 U.S.C. 119(a) nor 35 U.S.C. 120 places any restrictions or limitations as to how the claimed invention must be disclosed in the earlier application to comply with 35 U.S.C. 112(a). Accordingly, an application is entitled to rely upon the filing date of an earlier application, even if the earlier application itself incorporates essential material by reference to another document."

M.P.E.P. § 608.01(p)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

M.P.E.P. § 608.01(p)

"The reason for incorporation by reference practice with respect to applications which are to issue as U.S. patents is to provide the public with a patent disclosure which minimizes the public's burden to search for and obtain copies of documents incorporated by reference which may not be readily available. Through the Office's incorporation by reference policy, the Office ensures that reasonably complete disclosures are published as U.S. patents. The same policy concern does not apply where the sole purpose for which an applicant relies on an earlier U.S. or foreign application is to establish an earlier filing date. ***Incorporation by reference in the earlier application of (1) patents or applications published by foreign countries or regional patent offices, (2) nonpatent publications, (3) a U.S. patent or application which itself incorporates "essential material" by reference, or (4) a foreign application, is not critical in the case of a "benefit" application***."

M.P.E.P. § 608.01(p)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Neurent v. Foundry

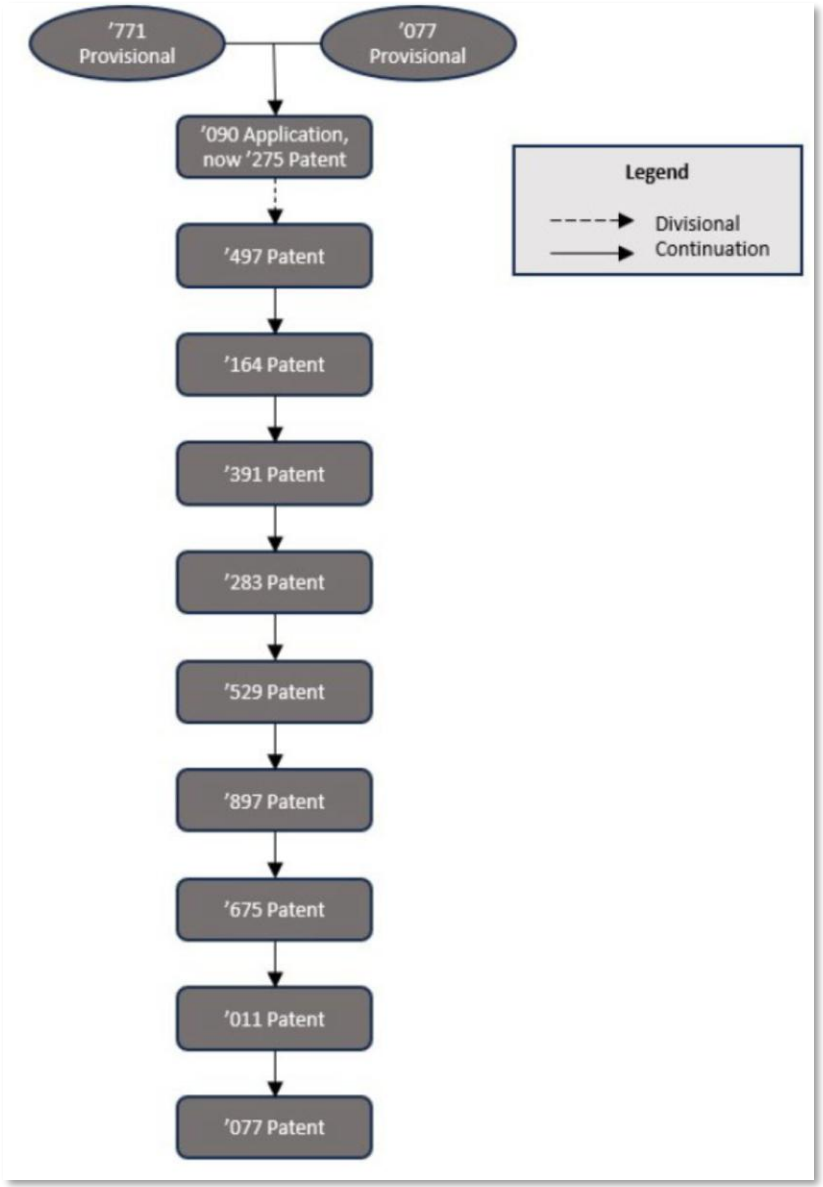
"[T]he introduction of subject matter from the '771 Provisional into the '893 Application, thereafter included in the '077 patent's specification ***does not constitute new matter because the '090 Application incorporates by reference the entirety of the '771 Provisional***."

Neurent Med. Inc. v. The Foundry, LLC, IPR2024-00669, Paper 8 at 16, 21-22 (P.T.A.B. July 23, 2024)

[11] The parties may also consider addressing other Board decisions where the interplay between Rule 1.57 and MPEP 608.01(p) is discussed. *See, e.g.*, *Neurent Medical Inc. v. The Foundry, LLC*, IPR2024-00669, Paper 8 at 21–22 (PTAB July 23, 2024) (finding, at institution, that a putative priority-benefit application may incorporate-by-reference essential material from a separate provisional application); *Samsung Elecs. v. Acquis LLC*, IPR2021-00608, Paper 10 at 8–10 (PTAB Dec. 8, 2021) (addressing a priority application's nested incorporation-by-reference of essential material and explaining that the Office has maintained the guidance in MPEP § 608.01(p) even after Rule 1.57(d) became effective).

IPR2025-00465, Paper 53 (Sur-Reply) at 10

IPR2025-00465, Paper 13 at 19 n.11



DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Donovan's New Opinions on the "dodecyl-β-D-maltoside"


UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PADAGIS US LLC,

Petitioner,

v.

NEURELIS, INC.,

Patent Owner.

Case No. IPR2025-00465
U.S. Patent No. 11,241,414

REPLY DECLARATION OF MAUREEN DONOVAN, PH.D. IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 11,241,414

PAGE 1

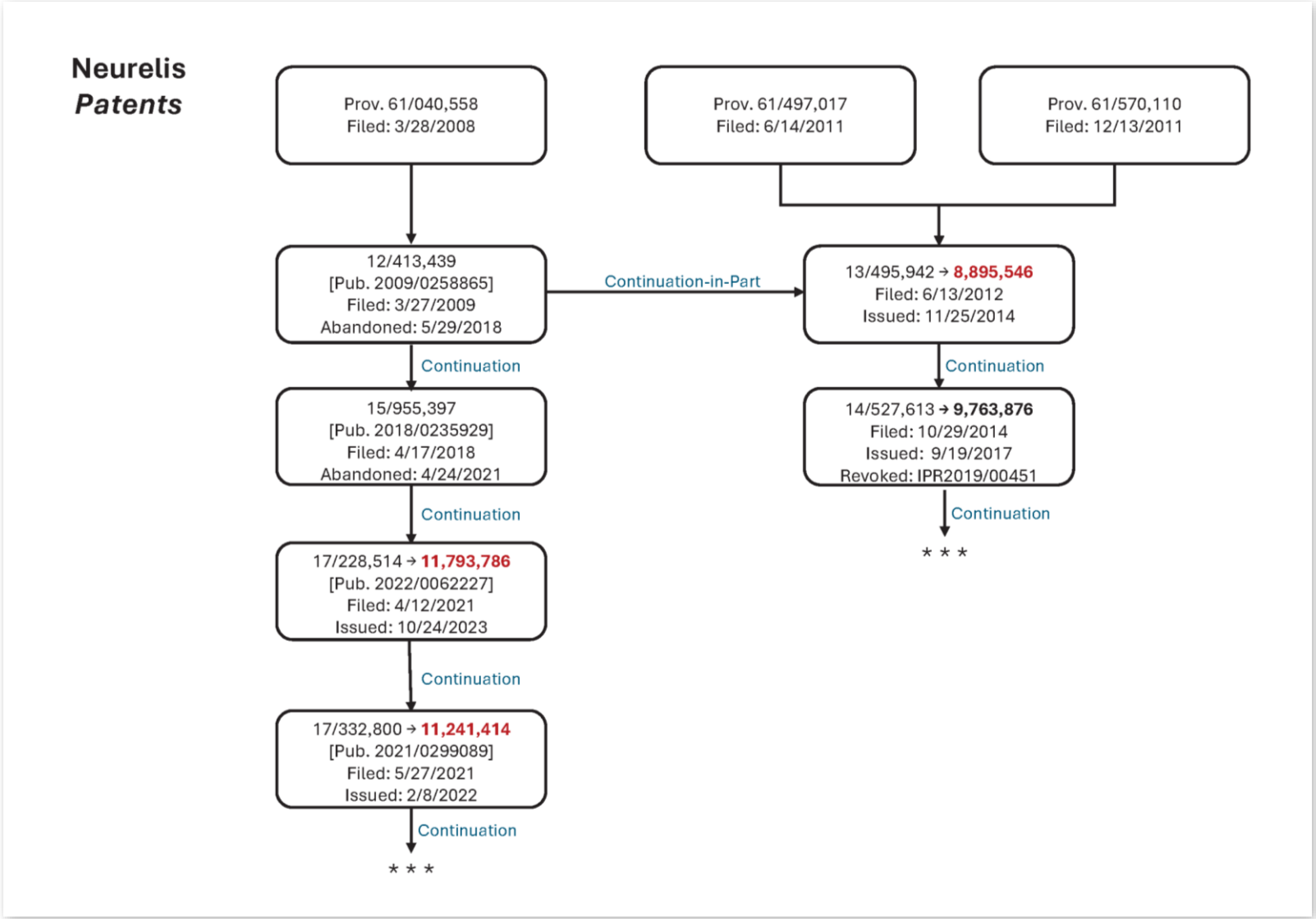
Padagis US LLC, EX1078

Donovan Reply Declaration EX1078

39. Further, Dr. Brown opines that "[e]ven if a skilled artisan would have considered Meezan, there would have been no reason to modify Gwozdz-PCT to add alkyl glycosides, let alone dodecyl maltoside, let alone *n*-dodecyl-β-D-maltoside (which is not even disclosed in Meezan)." Ex. 2073 (Brown Decl.) at ¶ 255. I disagree with Dr. Brown for a number of reasons, as explained below. Indeed, as I explained in my opening declaration, Meezan expressly discloses "dodecyl-β-D-maltoside" as a preferred penetration enhancer, where a POSA would have understood that to be a reference to "n-dodecyl-β-D-maltoside." *See, e.g.*, Ex. 1062 (Donovan Op. Decl.) at ¶¶ 90-93, 133-139.

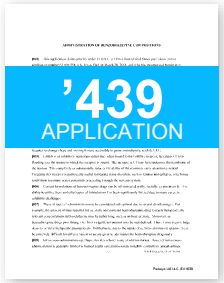
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Family Tree



DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

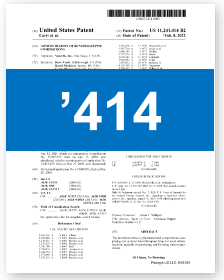
Disclosure of "dodecyl-β-D-maltoside"



trehalose. Exemplary alkyl glycosides that may be employed include octyl-, nonyl-, decyl-, undecyl-, dodecyl, tridecyl, tetradecyl, pentadecyl, octadecyl α- or β-D-maltoside, -glucoside or sucroside. In some embodiments, the preferred glycosides include maltose, sucrose or glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12, 14, 16, 18 or 20 carbon atoms. Where present, the amount of alkyl glycoside in the composition is

* * *

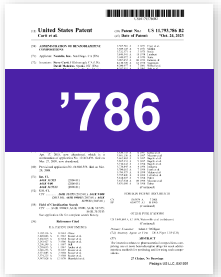
EX1039 ¶[056]



* * *

rose, sucrose and trehalose. Exemplary alkyl glycosides that may be employed include octyl-, nonyl-, decyl-, undecyl-, dodecyl, tridecyl, tetradecyl, pentadecyl, octadecyl α- or β-D-maltoside, -glucoside or sucroside. In some embodi-

'414 Patent at 13:43–49



rose, sucrose and trehalose. Exemplary alkyl glycosides that may be employed include octyl-, nonyl-, decyl-, undecyl-, dodecyl, tridecyl, tetradecyl, pentadecyl, octadecyl α- or β-D-maltoside, -glucoside or sucroside. In some embodi-

'786 Patent at 13:43–49

IPR2025-00465, Paper 53 (Sur-Reply) at 11–12; EX2073 ¶141

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Written Description of Compositions Including *n*-Dodecyl-β-D-Maltoside

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Not a "Blaze Marks" Case

"[A]dequate written description requires a precise definition, such as by structure, formula, ***chemical name***, physical properties, or other properties … sufficient to distinguish" the subject matter."

Ariad Pharms., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1350 (Fed. Cir. 2010) (*en banc*)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Not a "Blaze Marks" Case

"At the outset, we note that this is not a typical written description case. It is not a 'blaze marks' case in which the claims recite a species where the specification describes only a genus."

"Nor is it a case in which a patentee attempts to claim broadly that which the specification describes only narrowly."

Allergan UAS, Inc. v. MSN Lab'ys Priv. Ltd., 111 F.4th 1358, 1372 (Fed. Cir. 2024) (distinguishing *Purdue* and *Fujikawa*)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Not a "Blaze Marks" Case

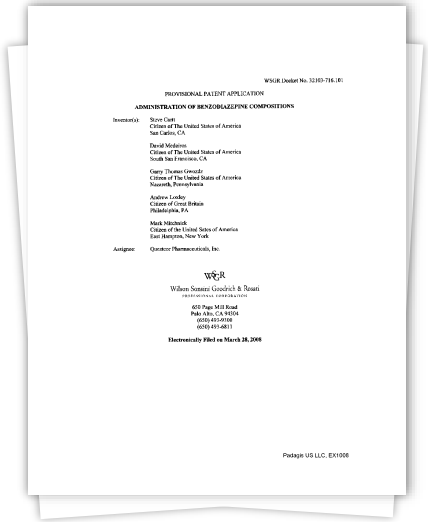
"Here, the asserted claims are essentially picture claims …. The claims are narrow, not only in that they recite specific amounts of the ingredients (in most cases, not even ranges), but also in that they recite specific ingredients."

"The claims do not recite an embodiment that is arguably undisclosed."

Allergan UAS, Inc. v. MSN Lab'ys Priv. Ltd., 111 F.4th 1358, 1372 (Fed. Cir. 2024) (distinguishing *Purdue* and *Fujikawa*)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

'558 Provisional



PROVISIONAL PATENT APPLICATION

ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

Inventor(s): Steve Ciotti
Citizen of The United States of America
San Carlos, CA

David Medanos
Citizen of The United States of America
South San Francisco, CA

Garry Thomas Gwozdz
Citizen of The United States of America
Nazareth, Pennsylvania

Andrew Lesley
Citizen of Great Britain
Philadelphia, PA

Mark Mitchnick
Citizen of the United Sates of America
East Hampton, New York

Assignee: Questcor Pharmaceuticals, Inc.

WSGR
Wilson Sonsini Goodrich & Rosati
PROFESSIONAL CORPORATION

650 Page Mill Road
Palo Alto, CA 94304
(650) 493-9300
(650) 493-6811

Electronically Filed on March 28, 2008

Pedagio US LLC, EX1008

'558 Provisional
EX1008

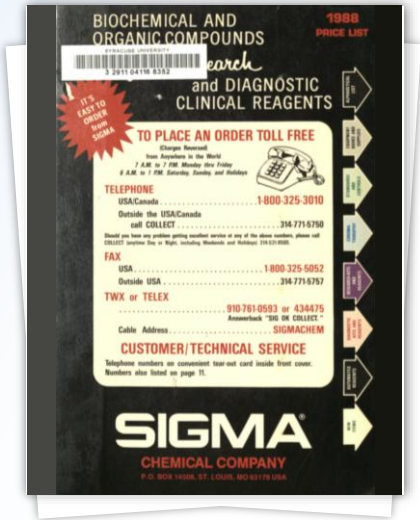
[150] In some embodiments, the drug delivery system of the invention may advantageously comprise an absorption enhancer. The term "enhancer", means any material which acts to increase absorption across the mucosa and/or increases bioavailability. In some embodiments, such materials include mucolytic agents,

17. The composition of one of claims 1 - 16, further comprising at least one additional ingredient selected from the group consisting of: active pharmaceutical ingredients; enhancers; excipients; and agents used to adjust the pH, buffer the composition, prevent degradation, and improve appearance, odor, or taste.

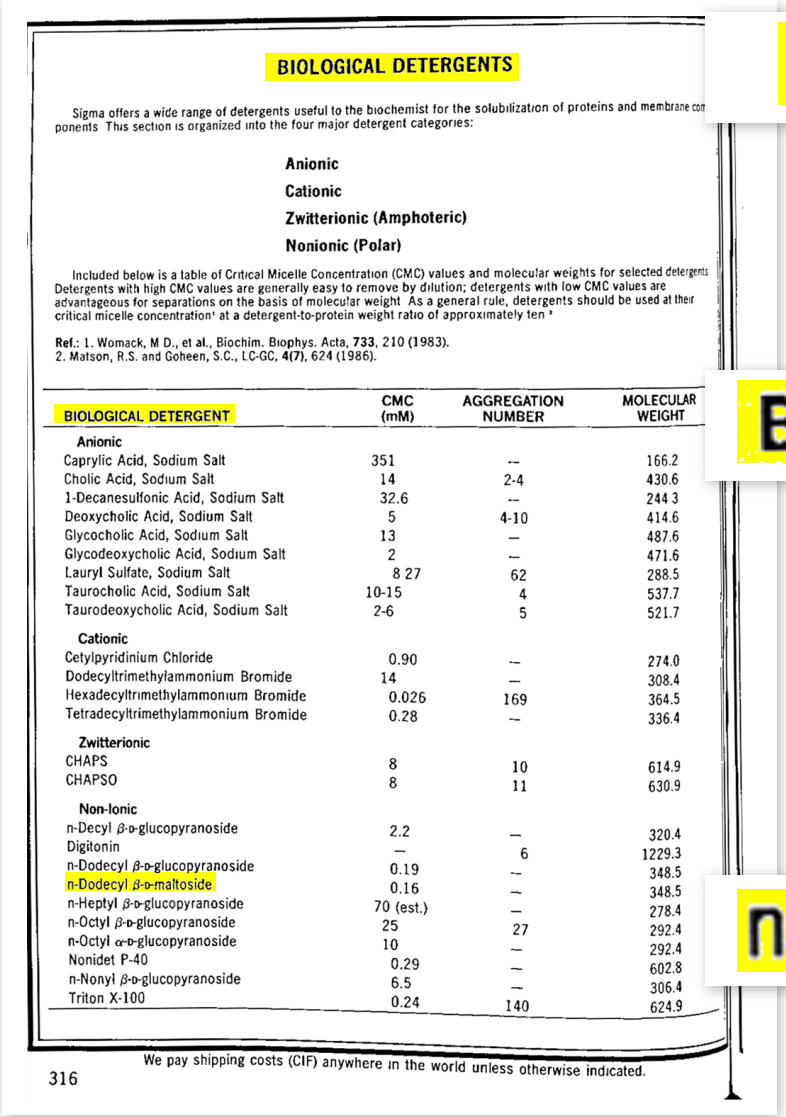
[152] In some embodiments, enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), acyl glycerols, fatty acids and salts, tyloxapol and biological detergents listed in the SIGMA Catalog, 1988, page 316-321 (which is incorporated herein by reference). Also agents that modify the membrane fluidity and permeability are appropriate such as enamines (e.g. phenylalanine enamine of ethylacetoacetate), malonates (e.g. diethyleneoxymethylene malonate), salicylates, bile salts and analogues and fusidates. Suitable concentrations are up to 20% w/v.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Sigma Catalog



Sigma Catalog
EX1026



BIOLOGICAL DETERGENTS

Sigma offers a wide range of detergents useful to the biochemist for the solubilization of proteins and membrane components. This section is organized into the four major detergent categories:

Anionic
Cationic
Zwitterionic (Amphoteric)
Nonionic (Polar)

Included below is a table of Critical Micelle Concentration (CMC) values and molecular weights for selected detergents. Detergents with high CMC values are generally easy to remove by dilution; detergents with low CMC values are advantageous for separations on the basis of molecular weight. As a general rule, detergents should be used at their critical micelle concentration[1] at a detergent-to-protein weight ratio of approximately ten.[2]

Ref.: 1. Womack, M.D., et al., Biochim. Biophys. Acta, **733**, 210 (1983).
2. Matson, R.S. and Goheen, S.C., LC-GC, **4(7)**, 624 (1986).

BIOLOGICAL DETERGENT	CMC (mM)	AGGREGATION NUMBER	MOLECULAR WEIGHT
Anionic			
Caprylic Acid, Sodium Salt	351	--	166.2
Cholic Acid, Sodium Salt	14	2-4	430.6
1-Decanesulfonic Acid, Sodium Salt	32.6	--	244.3
Deoxycholic Acid, Sodium Salt	5	4-10	414.6
Glycocholic Acid, Sodium Salt	13	--	487.6
Glycodeoxycholic Acid, Sodium Salt	2	--	471.6
Lauryl Sulfate, Sodium Salt	8.27	62	288.5
Taurocholic Acid, Sodium Salt	10-15	4	537.7
Taurodeoxycholic Acid, Sodium Salt	2-6	5	521.7
Cationic			
Cetylpyridinium Chloride	0.90	--	274.0
Dodecyltrimethylammonium Bromide	14	--	308.4
Hexadecyltrimethylammonium Bromide	0.026	169	364.5
Tetradecyltrimethylammonium Bromide	0.28	--	336.4
Zwitterionic			
CHAPS	8	10	614.9
CHAPSO	8	11	630.9
Non-Ionic			
n-Decyl β-D-glucopyranoside	2.2	--	320.4
Digitonin	--	6	1229.3
n-Dodecyl β-D-glucopyranoside	0.19	--	348.5
n-Dodecyl β-D-maltoside	0.16	--	348.5
n-Heptyl β-D-glucopyranoside	70 (est.)	--	278.4
n-Octyl β-D-glucopyranoside	25	27	292.4
n-Octyl α-D-glucopyranoside	10	--	292.4
Nonidet P-40	0.29	--	602.8
n-Nonyl β-D-glucopyranoside	6.5	--	306.4
Triton X-100	0.24	140	624.9

We pay shipping costs (CIF) anywhere in the world unless otherwise indicated.

316

BIOLOGICAL DETERGENT

n-Dodecyl β-D-maltoside

EX1026 (Sigma Catalog) at 19

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Disclosure in Sigma Catalog

Dr. Donovan

Q. Amongst that last category is listed "n-Dodecyl-beta-D-maltoside," correct?

A. Yes.

Q. A. person of ordinary skill would immediately discern that this is the same compound that is included in the claims of the '414 patent we looked at I think as the first document today, correct?

A. (Reviewing document.)

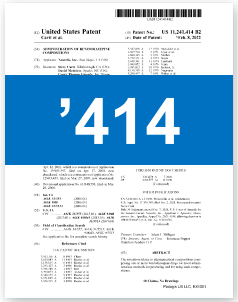
Q. The claims are in the back.

A. (Reviewing document.) Yes, it's the same compound listed in the claims of the 1001-414.

EX2070 at 178:20–179:7

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Express Disclosure



'414

What is claimed is:

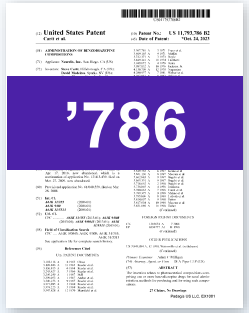
1. A pharmaceutical solution for nasal administration consisting of:

diazepam or a pharmaceutically acceptable salt thereof;

one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from 30% to 95% (w/w);

ethanol and benzyl alcohol in a combined amount from 10% to 70% (w/w); and

n-dodecyl beta-D-maltoside.



'786

What is claimed is:

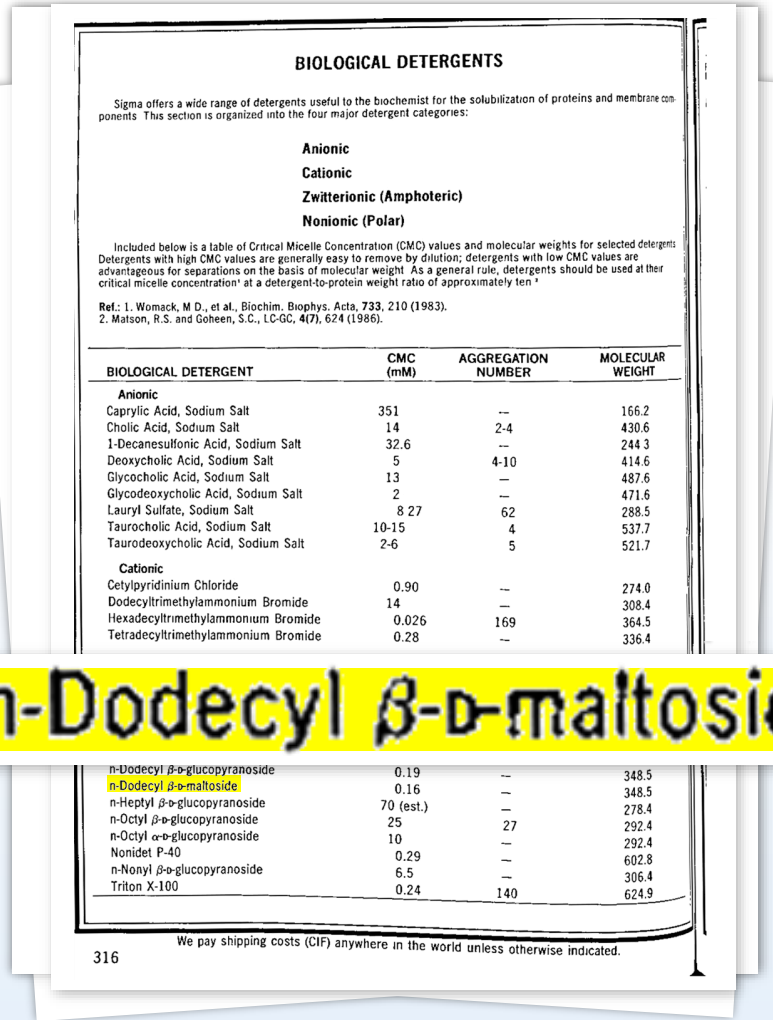
1. A pharmaceutical solution for nasal administration consisting of:

a therapeutically effective amount of diazepam or a pharmaceutically acceptable salt thereof;

one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any isomers thereof, any esters thereof, and any combinations thereof, in an amount from 30% to 95% (w/w);

one or more alcohols in an amount from 10% to 70% (w/w), wherein the one or more alcohols comprises benzyl alcohol; and

n-dodecyl beta-D-maltoside.



BIOLOGICAL DETERGENTS

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Triton X-100	0.24	140	624.9

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316

n-Dodecyl β-D-maltoside

Sigma Catalog
EX1026 at 19

IPR2025-00465, Paper 28 (POR) at 25-26

Agenda

- No Collateral Estoppel
- Priority Date of '414 and '786 Patents
- Claim Construction
- Non-Obviousness
  - Failure to Disclose All Limitations
  - No Motivation to Combine
- Priority Date of Gwozdz-PCT
- Cartt-'784
- Petitioner's Motion to Strike
- Patent Owner's Motion to Strike
- Patent Owner's Motion to Exclude

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Petitioner's District Court Position for "Consisting of"

'414 Patent
'786 Patent
'546 Patent

What is claimed is:

1. A pharmaceutical solution for nasal administration consisting of:

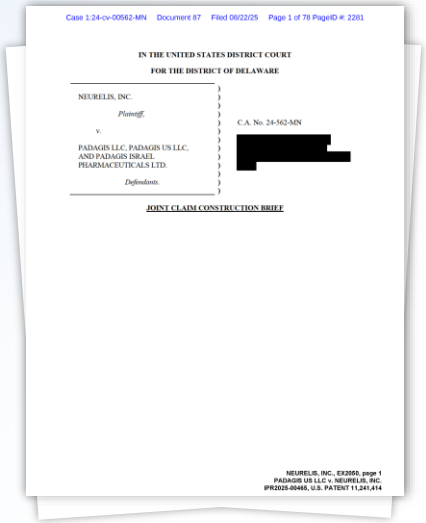
Joint Claim Construction Brief
EX2050 at 27

V. DISPUTED CONSTRUCTIONS

Term	Neurelis's Position	Padagis's Construction
A pharmaceutical solution for nasal administration consisting of	No construction necessary; the scope of "consisting of" is established by law.	"a pharmaceutical solution for nasal administration containing only those elements set forth in the claim and excluding anything else, particularly excluding water and oil" Otherwise indefinite.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Petitioner's Indefiniteness Contentions (District Court)


Case 1:24-cv-00562-MN Document 87 Filed 08/22/25 Page 1 of 78 PageID #: 2281

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NEURELIS, INC.
Plaintiff,
v.
PADAGIS LLC, PADAGIS US LLC, AND PADAGIS ISRAEL PHARMACEUTICALS LTD.
Defendants.

C.A. No. 24-562-MN [redacted]

JOINT CLAIM CONSTRUCTION BRIEF

NEURELIS, INC., EX2050, page 1
PADAGIS US LLC v. NEURELIS, INC.
IPR2025-00465, U.S. PATENT 11,241,414

Joint CC Brief EX2050

If Neurelis is correct, and the claims can include related, unrecited and disclaimed elements such as water, then the claims are indefinite because a POSA would not be able to determine with reasonable certainty when a composition would begin to infringe. If other related, but unrecited,

If the Asserted Claims are construed to include other potential ingredients, such as water and oil, then all of the Asserted Claims are invalid as indefinite because they fail to inform with reasonable certainty the extent to which the claims include such ingredients, if at all. Each Asserted

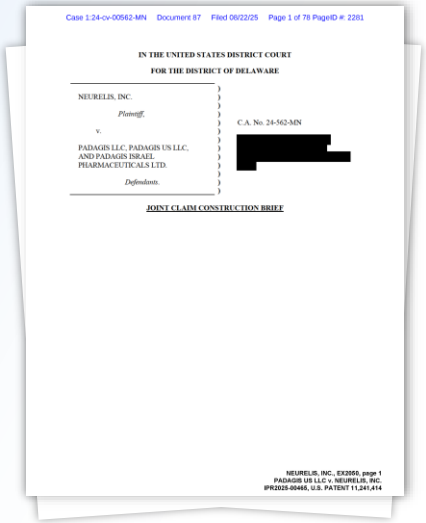
alleged invention. The specification's few examples of formulations having water included in relatively small amounts, suggests that even miniscule amounts can be material. Thus, the exclusion of water, oil, and the other ingredients is not only consistent with, but required by [caselaw].

EX2050 (Joint CC Br.) at 41, 46, 53

IPR2025-00465, Paper 28 (POR) at 11, 43, Paper 53 (Sur-Reply) at 20

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Donovan's District Court Contentions


Case 1:24-cv-00562-MN Document 87 Filed 08/22/25 Page 1 of 78 PageID #: 2281

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NEURELIS, INC.
Plaintiff,
v.
PADAGIS LLC, PADAGIS US LLC, AND PADAGIS ISRAEL PHARMACEUTICALS LTD.
Defendants.

C.A. No. 24-562-MN [redacted]

JOINT CLAIM CONSTRUCTION BRIEF

NEURELIS, INC., EX2050, page 1
PADAGIS US LLC v. NEURELIS, INC.
IPR2025-00465, U.S. PATENT 11,241,414

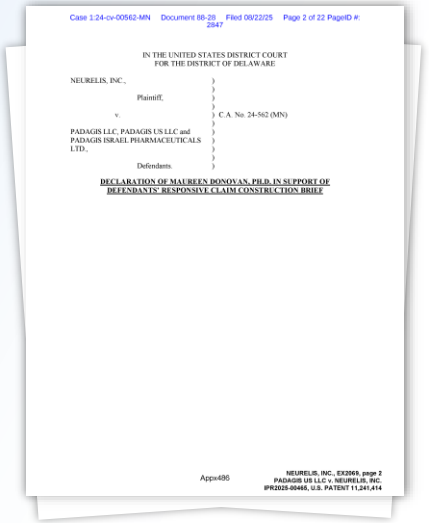
Joint CC Brief
EX2050

Water is not, however, an inert ingredient. *See* '546 patent at Table 11-3 (reporting different pharmacokinetic values in formulations having and not having water). As Dr. Donovan explains, given the solubility challenges of benzodiazepines, the presence and relative amount of water can significantly affect the performance of a formulation. Donovan Decl. at ¶52 ("[T]he amount of water present in the claimed solutions is a very important factor, as it impacts the solubility of the benzodiazepine within the claimed solution")]. Whether and how much water to include is a reflection of intentional design choices. Donovan Decl. at ¶30.

EX2050 (Joint CC Br.) at 55

IPR2025-00465, Paper 28 (POR) at 11, Paper 53 (Sur-Reply) at 20

Donovan's District Court Declaration



Case 1:24-cv-00562-MN Document 88-28 Filed 08/22/25 Page 2 of 22 PageID #: 2847

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NEURELIS, INC.,
Plaintiff,
v.
C.A. No. 24-562 (MN)
PADAGIS LLC, PADAGIS US LLC and PADAGIS ISRAEL PHARMACEUTICALS LTD.,
Defendants.

DECLARATION OF MAUREEN DONOVAN, PH.D. IN SUPPORT OF DEFENDANTS' RESPONSIVE CLAIM CONSTRUCTION BRIEF

Appx486

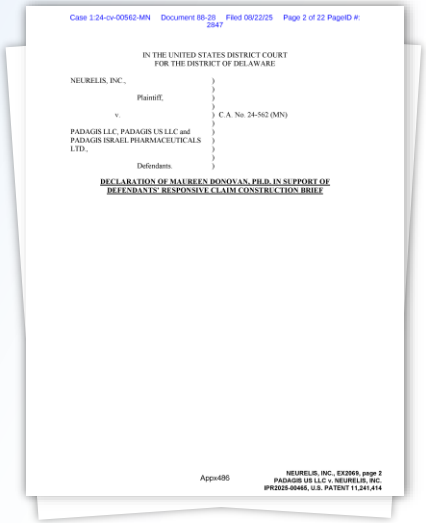
NEURELIS, INC., EX2069, page 2
PADAGIS US LLC v. NEURELIS, INC.
IPR2025-00465, U.S. PATENT 11,241,414

Donovan Declaration EX2069

26. It is my opinion that water content (even very small amounts of water) is not an "impurity ordinarily associated" with the claimed solution, and that water content is not "unrelated to" the alleged invention. Consequently, based on the case law cited by Neurelis and Dr. McConville, it is my opinion that the "consisting of" transition language of the Asserted Patents does not allow for the inclusion of small amounts of water. The basis for this determination is provided in the sections that follow.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Donovan's District Court Declaration



Case 1:24-cv-00562-MN Document 88-28 Filed 08/22/25 Page 2 of 22 PageID #: 2847

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NEURELIS, INC.,
Plaintiff,
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C.A. No. 24-562 (MN)
PADAGIS LLC, PADAGIS US LLC and PADAGIS ISRAEL PHARMACEUTICALS LTD.,
Defendants.

DECLARATION OF MAUREEN DONOVAN, PH.D. IN SUPPORT OF DEFENDANTS' RESPONSIVE CLAIM CONSTRUCTION BRIEF

Appx486

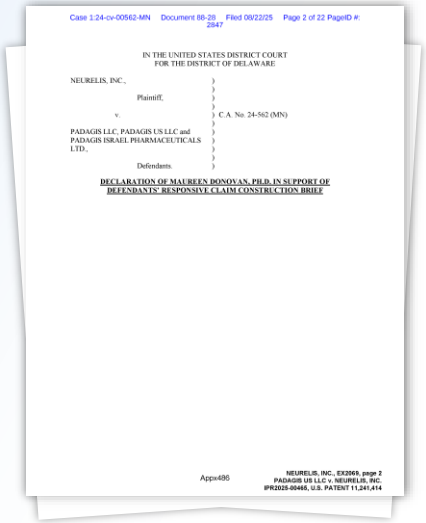
NEURELIS, INC., EX2069, page 2
PADAGIS US LLC v. NEURELIS, INC.
IPR2025-00465, U.S. PATENT 11,241,414

Donovan Declaration
EX2069

50. As I discussed in the section on legal principles, it is my understanding a patent is invalid for indefiniteness if its claims, when read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention. For the reasons I have articulated previously, it is my opinion that water content (even very small amounts of water) is not an "impurity ordinarily associated" with the claimed solution, and that water and oil content are not "unrelated to" the alleged invention, meaning that the "consisting of" transition phrase does not allow for small amounts of water in the claimed solutions. However, should the claims of the Asserted Patents be construed to allow for the inclusion of water (and other components), it is my opinion that a POSA cannot reasonably ascertain what is within the scope of the invention, and what is outside the scope of the invention, and the claims are indefinite.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Donovan's District Court Declaration


Case 1:24-cv-00562-MN Document 88-28 Filed 08/22/25 Page 2 of 22 PageID #: 2847

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NEURELIS, INC.,
Plaintiff,
v. C.A. No. 24-562 (MN)
PADAGIS LLC, PADAGIS US LLC and PADAGIS ISRAEL PHARMACEUTICALS LTD.,
Defendants.

DECLARATION OF MAUREEN DONOVAN, PH.D. IN SUPPORT OF DEFENDANTS' RESPONSIVE CLAIM CONSTRUCTION BRIEF

Appx486

NEURELIS, INC., EX2069, page 2
PADAGIS US LLC v. NEURELIS, INC.
IPR2025-00465, U.S. PATENT 11,241,414

Donovan Declaration EX2069

57. Taken together, it is my opinion that the Asserted Patents do not provide any guidance regarding what additional unrecited components (whether it be water or other excipients) are "unrelated to the invention" and are allowed in the claimed solutions or are "related" to the invention and are excluded from the claimed solutions. Such a determination is arbitrary and will likely vary from one POSA to another. Additionally, the Asserted Patents do not provide any guidance regarding what amount of water (or other unrecited components) constitutes a "trace amount" and may be present in the claimed solutions, or what amount of water (or other unrecited components) rise to the level of an "ingredient" and is excluded from the claimed solutions. For at least these reasons, it is my opinion that a POSA does not have reasonable certainty as to what is within the scope of the Asserted Patent claims, and the claims are indefinite.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Timeline of Shifting Constructions

DISTRICT COURT

July 11, 2025
Donovan signs declaration, asserting indefiniteness and construction of "consisting of"
[EX2069]

August 15, 2025
Padagis files joint claim construction brief, asserting indefiniteness and construction of "consisting of"
[EX2050]

March 30, 2026
Padagis files stipulation on "consisting of"
[EX1083]

January | July | August | September | December | January | February | March
2025 | 2026

PTAB

January 17, 2025
Padagis files IPR petition with Donovan declaration, and does not construe "consisting of"
[Paper 2; EX1062]

September 16, 2025
Institution Decision
[Paper 13]

January 5, 2026
Patent Owner's Response
[Paper 28]

March 31, 2026
Padagis replies to POR with new Donovan declaration
[Paper 43; EX1078]

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Timeline of Shifting Constructions

DISTRICT COURT

July 11, 2025
Donovan signs declaration, asserting indefiniteness and construction of "consisting of"
[EX2069]

August 15, 2025
Padagis files joint claim construction brief, asserting indefiniteness and construction of "consisting of"
[EX2050]

May 8, 2026
Defendants serve invalidity contentions, asserting indefiniteness of "consisting of"
[EX1107]

March 30, 2026
Padagis files stipulation on "consisting of"
[EX1083]

January | July | August | September | December | January | February | March | April | May
2025 | 2026

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[Paper 2; EX1062]

September 16, 2025
Institution Decision
[Paper 13]

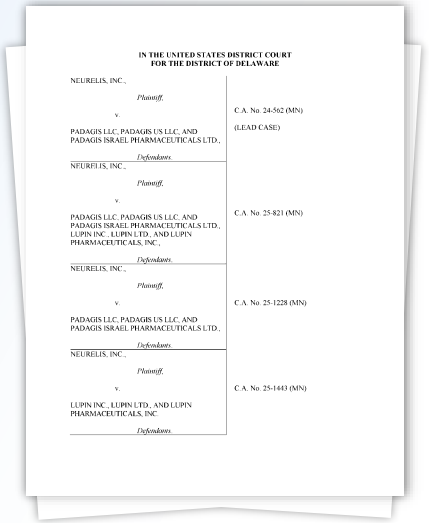
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[Paper 28]

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PTAB

IPR2025-00465, Paper 53 (Sur-Reply) at 20-22

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE



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Plaintiff,
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PADAGIS LLC, PADAGIS US LLC, AND PADAGIS ISRAEL PHARMACEUTICALS LTD.,
Defendants.
C.A. No. 24-562 (MN)
(LEAD CASE)

NEURELIS, INC.,
Plaintiff,
v.
PADAGIS LLC, PADAGIS US LLC, AND PADAGIS ISRAEL PHARMACEUTICALS LTD., LUPIN INC., LUPIN LTD., AND LUPIN PHARMACEUTICALS, INC.,
Defendants.
C.A. No. 25-821 (MN)

NEURELIS, INC.,
Plaintiff,
v.
PADAGIS LLC, PADAGIS US LLC, AND PADAGIS ISRAEL PHARMACEUTICALS LTD.,
Defendants.
C.A. No. 25-1228 (MN)

NEURELIS, INC.,
Plaintiff,
v.
LUPIN INC., LUPIN LTD., AND LUPIN PHARMACEUTICALS, INC.
Defendants.
C.A. No. 25-1443 (MN)

Defendants' Preliminary Invalidity Contentions

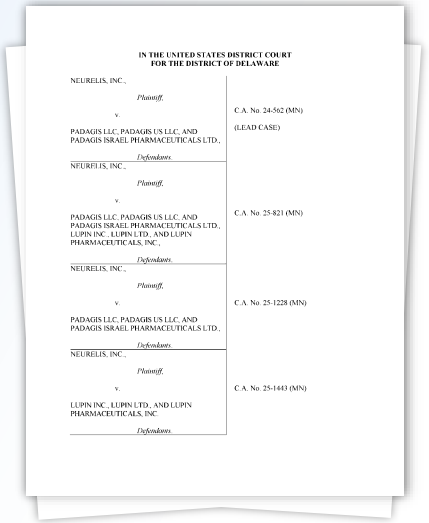
[3] In addition, Amneal adopts the preliminary invalidity contentions with respect to the '414 patent and '786 patent previously served by Padagis on December 20, 2024 as well as the preliminary invalidity contentions served by Padagis and Lupin with respect to the '414, '786, '664, '852, and '061 patents on February 6, 2026, and fully incorporates those positions as to Amneal as if set forth herein.

Defendants' Preliminary Invalidity Contentions at 8 n.3

[20] In addition, Lupin adopts the preliminary invalidity contentions with respect to the '414 patent and '786 patent previously served by Padagis on December 20, 2024, and fully incorporates those positions as if set forth herein.

Defendants' Preliminary Invalidity Contentions at 188 n.20

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE



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FOR THE DISTRICT OF DELAWARE

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Plaintiff,
v.
PADAGIS LLC, PADAGIS US LLC, AND PADAGIS ISRAEL PHARMACEUTICALS LTD.,
Defendants.
C.A. No. 25-1228 (MN)

NEURELIS, INC.,
Plaintiff,
v.
LUPIN INC., LUPIN LTD., AND LUPIN PHARMACEUTICALS, INC.
Defendants.
C.A. No. 25-1443 (MN)

Defendants' Preliminary Invalidity Contentions

1. The Phrase "Pharmaceutical Solution Consisting Of" Is Indefinite

As Padagis explained in its preliminary invalidity contentions with respect to the '546, '414, and '786 patents, to the extent the claims of the '546, '414, and '786 patents allow for the presence of water, the phrase "pharmaceutical solution consisting of" is indefinite because a POSA would lack reasonable certainty about whether the claimed "pharmaceutical solution" can contain water. *See* Padagis's Initial Inv. Contentions at 33-36. For the same reasons discussed in Padagis's preliminary invalidity contentions with respect to the '546, '414, and '786 patents, the phrase "pharmaceutical solution consisting of" recited in the claims of the '852 patent is indefinite.[40] *Id.*

Indeed, like the claims of the '546, '414, and '786 patents, all claims of the '852 patent recite either a "pharmaceutical solution consisting of" specific amounts of Vitamin E, diazepam, DDM, benzyl alcohol, and ethanol. *Supra* Sections II.E.1. To reiterate, the transitional phrase "consisting of" is a term of patent convention meaning that the claimed invention contains only what is expressly set forth in the claim." *Multilayer Stretch Cling Film Holdings, Inc. v. Berry*

EX1107, Defendants' Preliminary Invalidity Contentions at 328

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Terumo v. Haemonetics (informative)

"Patent Owner argues that ***in its Petitions, Petitioner states the claims 'need no construction'*** and advances a plain and ordinary meaning for all claim terms, ***but that one week after institution, Petitioner argued in district court invalidity contentions that certain claims of the each of the challenged patents reciting a 'controller' are indefinite***."

"As I have stated repeatedly, a petitioner should present a single construction and apply that construction consistently before the Board and the district court."

Terumo BCT Inc. v. Haemonetics Corp., IPR2025-01374, Paper 20 (P.T.A.B. May 12, 2026) (informative)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

TikTok v. Shopsee (informative)

"In the Petition, Petitioner states that '[n]o express constructions are required to find the [challenged] claims invalid.'"

"***Petitioner asserted certain claim terms are indefinite in district court and does not explain why different claim construction positions between district court and the Board are warranted***…."

"Petitioner responds that it 'has now stipulated that it will not pursue the aforesaid indefiniteness arguments if this proceeding is instituted.'"

"Petitioner has stipulated that it will continue to pursue different constructions and abandon the inconsistent construction in district court if the IPR is instituted. This is not in keeping with our precedent, and I decline to modify it to permit this approach."

TikTok, Inc. v. Shopsee, Inc., IPR2025-01485, Paper 13 (Jan. 16, 2026) (informative)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ford Motor v. AutoConnect (informative)

"***Patent Owner argues that Petitioner advances a 'plain and ordinary meaning' for claim terms in the Petitions, but recently served invalidity contentions in the related district court proceedings that argued all the challenged claims are indefinite***."

"In its briefing, Petitioner states that it will stipulate to withdraw all indefiniteness arguments against the challenged patents from the related litigation if the Board agrees to maintain and not vacate institution of these IPRs.…This stipulation, which Petitioner offered only after Petitioner's actions ran afoul of *Revvo* and *Tesla* and only after Patent Owner brought those actions to the Office's attention, is insufficient."

Ford Motor Co. v. AutoConnect Holdings LLC, IPR2025-01342, Paper 27 at 2–3 (P.T.A.B. May 12, 2026) (informative)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Magnolia Med. v. Kurin (precedential)

"[P]arties seemingly take inconsistent positions, without sufficient reasoning, on overlapping issues between district court and the PTAB, suggesting that parties are misleading one tribunal or the other or pursuing alternative theories under a 'wait and see' approach presumably to gain a litigation advantage and/or settlement leverage."

Magnolia Med. Techs., Inc. v. Kurin, Inc., IPR2026-00097, Paper 17 at 4 (P.T.A.B. May 14, 2026) (precedential)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Agenda

- No Collateral Estoppel
- Priority Date of '414 and '786 Patents
- Claim Construction
- Non-Obviousness
  - Failure to Disclose All Limitations
  - No Motivation to Combine
- Priority Date of Gwozdz-PCT
- Cartt-'784
- Petitioner's Motion to Strike
- Patent Owner's Motion to Strike
- Patent Owner's Motion to Exclude

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Asserted References

'414 Patent
'786 Patent
'546 Patent

Inventors: **Steve Cartt**, Hillsborough, CA (US); **David Medeiros**, Sparks, NV (US); **Garry Thomas Gwozdz**, Jim Thorpe, PA (US); **Andrew Loxley**, Brussels (BE); **Mark Mitchnick**, East Hampton, NY (US); **David F. Hale**, San Diego, CA (US); **Edward T. Maggio**, San Diego, CA (US)

WO2009/120933
Gwozdz-PCT
EX1009

Inventors; and
Inventors/Applicants *(for US only)*: **GWOZDZ, Garry, Thomas** [US/US]; 329 South Main Street, Nazareth, PA 18064 (US). **LOXLEY, Andrew** [GB/US]; 126 Market Street, #5, Philadelphia, PA 19106 (US). **MITCHNICK, Mark** [US/US]; 80 Three Mile Harbor Drive, East Hampton, NY 11937 (US).

US2006/0046962
Meezan
EX1010

Inventors: **Elias Meezan**, Birmingham, AL (US); **Dennis J. Pillion**, Hoover, AL (US); **Edward T. Maggio**, San Diego, CA (US)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Non-Obviousness: "consisting of"

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

All Claims Require "Consisting of"

'414 Patent
'786 Patent
'546 Patent

What is claimed is:

1. A pharmaceutical solution for nasal administration consisting of:

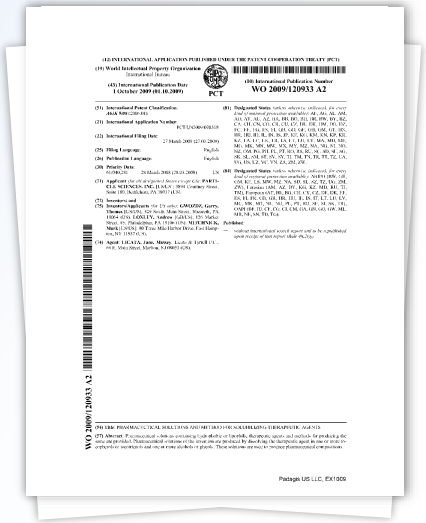
Joint Claim Construction Brief
EX2050 at 27

V. DISPUTED CONSTRUCTIONS

Term	Neurelis's Position	Padagis's Construction
A pharmaceutical solution for nasal administration consisting of	No construction necessary; the scope of "consisting of" is established by law.	"a pharmaceutical solution for nasal administration containing only those elements set forth in the claim and excluding anything else, particularly excluding water and oil" Otherwise indefinite.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Water in Gwozdz-PCT



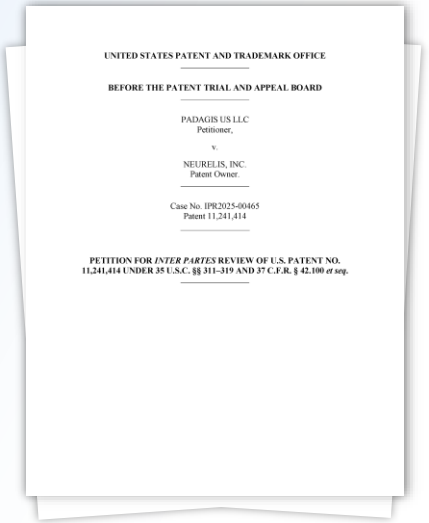
Gwozdz-PCT
EX1009

The instant pharmaceutical solutions comprising a therapeutic agent, one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols can also be formulated into a pharmaceutical composition for injection by combining the instant pharmaceutical solution with, *e.g.*, saline solution or water and a Vitamin E solubilizing agent such as Cremophor. Such pharmaceutical compositions may further contain other pharmaceutically acceptable additives such as, but not limited to, acidifying, alkalizing, buffering, chelating, complexing and solubilizing agents, antioxidants and antimicrobial preservatives, penetration enhancers, humectants, suspending and/or viscosity modifying agents, tonicity and wetting or other biocompatible materials.

EX1009 (Gwozdz-PCT) at 10:3-16

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Water in Gwozdz-PCT



UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PADAGIS US LLC
Petitioner,

v.

NEURELIS, INC.
Patent Owner.

Case No. IPR2025-00465
Patent 11,241,414

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 11,241,414 UNDER 35 U.S.C. §§ 311–319 AND 37 C.F.R. § 42.100 *et seq.*

Petition
Paper 2

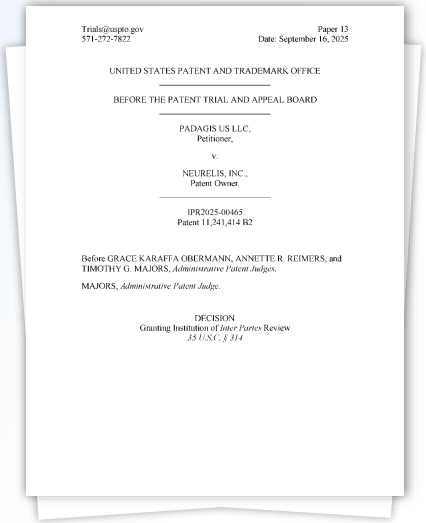
Moreover, a motivation existed to combine the teachings of Meezan related to alkyl glycosides with the pharmaceutical solutions described in Gwozdz. Gwozdz teaches that the pharmaceutical solutions described therein may further incorporate additional pharmaceutically acceptable additives, including, "acidifying, alkalizing, buffering, chelating, complexing and solubilizing agents, antioxidants and antimicrobial preservatives, penetration enhancers, humectants, suspending and/or viscosity modifying agents, tonicity and wetting or other biocompatible materials" to improve the efficacy. *Id.*, 10:12-16; EX1062, ¶97. Meezan is directed to

IPR2025-00465, Paper 2 (Petition) at 27

IPR2025-00465, Paper 2 (Petition) at 27

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Water in Gwozdz-PCT



Trials@uspto.gov
571-272-7822

Paper 13
Date: September 16, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PADAGIS US LLC,
Petitioner,

v.

NEURELIS, INC.,
Patent Owner.

IPR2025-00465
Patent 11,241,414 B2

Before GRACE KARAFFA OBERMANN, ANNETTE R. REIMERS, and TIMOTHY G. MAJORS, *Administrative Patent Judges*.

MAJORS, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

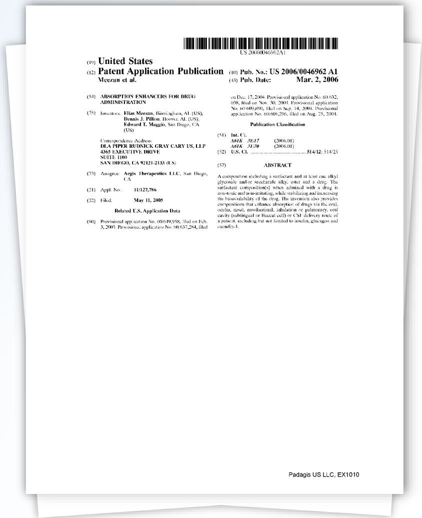
Institution Decision
Paper 13

drugs (e.g., diazepam) can be difficult to administer due to the drugs' limited solubility. *Id.* at 25–26 (citing Ex. 1001, 1:47–51). Gwozdz, Petitioner explains, teaches one approach to improve the solubility of benzodiazepines and, thus, drug delivery to nasal membranes, which involves dissolving difficult-to-solubilize therapeutic agents in solvents containing, for example, tocopherols and alcohols. *Id.* at 26 (citing Ex. 1009 7:29–34, 9:19–22; Ex. 1062 ¶¶ 94–96). Petitioner contends that Gwozdz teaches other additives may also be included to improve efficacy. *Id.* at 27 (citing Ex. 10:12–16; Ex. 1062 ¶ 97).

IPR2025-00465, Paper 13 (Institution Decision) at 32

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Water in Meezan


(19) United States
(12) Patent Application Publication
Meezan et al.
(10) Pub. No.: US 2006/0046962 A1
(43) Pub. Date: Mar. 2, 2006

(54) ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION

(75) Inventors: Elias Meezan, Birmingham, AL (US); Dennis J. Pillion, Hoover, AL (US); Edward T. Maggio, San Diego, CA (US)

Correspondence Address:
DLA PIPER RUDNICK GRAY CARY US, LLP
4365 EXECUTIVE DRIVE
SUITE 1100
SAN DIEGO, CA 92121-2133 (US)

(73) Assignee: Aegis Therapeutics LLC, San Diego, CA

(21) Appl. No.: 11/127,786

(22) Filed: May 11, 2005

Related U.S. Application Data

(60) Provisional application No. 60/649,958, filed on Feb. 3, 2005. Provisional application No. 60/637,284, filed on Dec. 17, 2004. Provisional application No. 60/632,038, filed on Nov. 30, 2004. Provisional application No. 60/609,890, filed on Sep. 14, 2004. Provisional application No. 60/604,296, filed on Aug. 25, 2004.

Publication Classification

(51) Int. Cl.
A61K 38/17 (2006.01)
A61K 31/70 (2006.01)
(52) U.S. Cl. 514/12; 514/25

(57) ABSTRACT

A composition including a surfactant and at least one alkyl glycoside and/or saccharide alkyl ester and a drug. The surfactant composition(s) when admixed with a drug is non-toxic and non-irritating, while stabilizing and increasing the bioavailability of the drug. The invention also provides compositions that enhance absorption of drugs via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell) or CSF delivery route of a patient, including but not limited to insulin, glucagon and exendin-4.

Padagis US LLC, EX1010

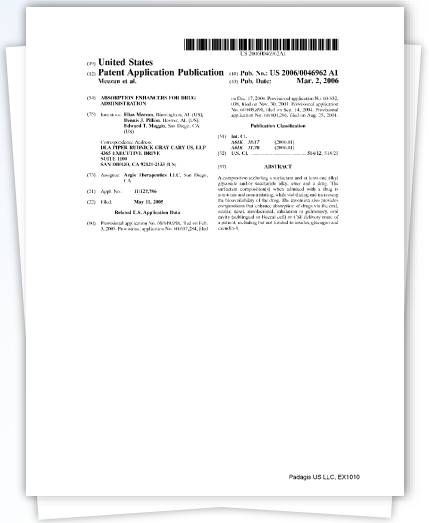
Meezan
EX1010

[0074] Additionally, the therapeutic compositions of the invention can consist of a pharmaceutically acceptable carrier. A "pharmaceutically acceptable carrier" is an aqueous or non-aqueous agent, for example alcoholic or oleaginous, or a mixture thereof, and can contain a surfactant, emollient, lubricant, stabilizer, dye, perfume, preservative, acid or base for adjustment of pH, a solvent, emulsifier, gelling agent, moisturizer, stabilizer, wetting agent, time release agent, humectant, or other component commonly included in a particular form of pharmaceutical composition. Pharmaceutically acceptable carriers are well known in the art and include, for example, aqueous solutions such as water or physiologically buffered saline or other solvents or vehicles such as glycols, glycerol, and oils such as olive oil or injectable organic esters. A pharmaceutically acceptable

EX1010 ¶0074

IPR2025-00465, Paper 53 (Sur-Reply) at 28

Water in Meezan



Meezan
EX1010

BACKGROUND INFORMATION

[0003] Therapeutic agents are often combined with various surfactants. Yet, surfactants are frequently irritating to the skin and other tissues, including mucosal membranes such as those found in the nose, mouth, eye, vagina, rectum, esophagus, intestinal tract, and the like. Many surfactants

EX1010 ¶0003

[0053] The therapeutic composition of the invention includes a drug and a drug absorption enhancing agent, for example, a surfactant. The term "surfactant" is any surface active agent that modifies interfacial tension of water. Typically, surfactants have one lipophilic and one hydrophilic group in the molecule. Broadly, the group includes soaps,

EX1010 ¶0053

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

"One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art . . . ."

In re Fine, 837 F.2d 1071, 1075 (Fed. Cir. 1998)

"[W]hether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, in making the combination available"

In re Fulton, 391 F.3d 1195, 1200 (Fed. Cir. 2004)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Non-Obviousness: *n*-dodecyl β-D-maltoside

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

"The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight."

Otsuka Pharm. Co., Ltd. v. Sandoz, Inc., 678 F.3d 1280, 1296 (Fed. Cir. 2012)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

"What matters is the path that the person of ordinary skill in the art would have followed, as evidenced by the pertinent prior art…."

Millenium Pharms., Inc. v. Sandoz Inc., 862 F.3d 1356, 1367 (Fed. Cir. 2017)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE



"Care must be taken to avoid hindsight reconstruction by using the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit."

In re NTP, Inc., 654 F.3d 1279, 1299 (Fed. Cir. 2011)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Asserted References ('414 and '546 Patents)

'414 Patent
'546 Patent

Inventors: **Steve Cartt**, Hillsborough, CA (US); **David Medeiros**, Sparks, NV (US); **Garry Thomas Gwozdz**, Jim Thorpe, PA (US); **Andrew Loxley**, Brussels (BE); **Mark Mitchnick**, East Hampton, NY (US); **David F. Hale**, San Diego, CA (US); **Edward T. Maggio**, San Diego, CA (US)

WO2009/120933
Gwozdz-PCT
EX1009

Inventors; and
Inventors/Applicants *(for US only)*: **GWOZDZ, Garry, Thomas** [US/US]; 329 South Main Street, Nazareth, PA 18064 (US). **LOXLEY, Andrew** [GB/US]; 126 Market Street, #5, Philadelphia, PA 19106 (US). **MITCHNICK, Mark** [US/US]; 80 Three Mile Harbor Drive, East Hampton, NY 11937 (US).

US2006/0046962
Meezan
EX1010

Inventors: **Elias Meezan**, Birmingham, AL (US); **Dennis J. Pillion**, Hoover, AL (US); **Edward T. Maggio**, San Diego, CA (US)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Asserted References ('786 Patent)

'786 Patent

Inventors: **Steve Cartt**, Hillsborough, CA (US); **David Medeiros**, Sparks, NV (US); **Garry Thomas Gwozdz**, Jim Thorpe, PA (US); **Andrew Loxley**, Brussels (BE); **Mark Mitchnick**, East Hampton, NY (US); **David F. Hale**, San Diego, CA (US); **Edward T. Maggio**, San Diego, CA (US)

WO2009/120933
Gwozdz-PCT
EX1009

Inventors; and
Inventors/Applicants *(for US only)*: **GWOZDZ, Garry, Thomas** [US/US]; 329 South Main Street, Nazareth, PA 18064 (US). **LOXLEY, Andrew** [GB/US]; 126 Market Street, #5, Philadelphia, PA 19106 (US). **MITCHNICK, Mark** [US/US]; 80 Three Mile Harbor Drive, East Hampton, NY 11937 (US).

US2006/0046962
Meezan
EX1010

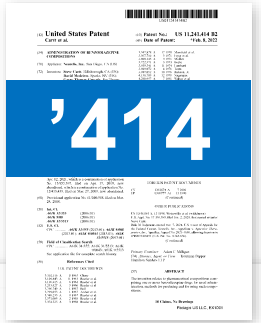
Inventors: **Elias Meezan**, Birmingham, AL (US); **Dennis J. Pillion**, Hoover, AL (US); **Edward T. Maggio**, San Diego, CA (US)

US2008/0279784
Cartt-2008
EX1065

Inventors: **Steve Cartt**, Union City, CA (US); **David Medeiros**, South San Francisco, CA (US)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Requirements for "n-dodecyl beta-D-maltoside"



What is claimed is:

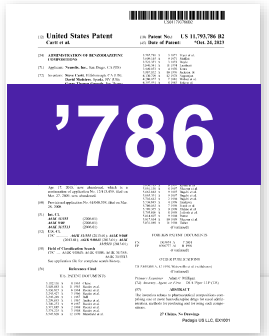
1. A pharmaceutical solution for nasal administration consisting of:

diazepam or a pharmaceutically acceptable salt thereof;

one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from 30% to 95% (w/w);

ethanol and benzyl alcohol in a combined amount from 10% to 70% (w/w); and

n-dodecyl beta-D-maltoside.



What is claimed is:

1. A pharmaceutical solution for nasal administration consisting of:

a therapeutically effective amount of diazepam or a pharmaceutically acceptable salt thereof;

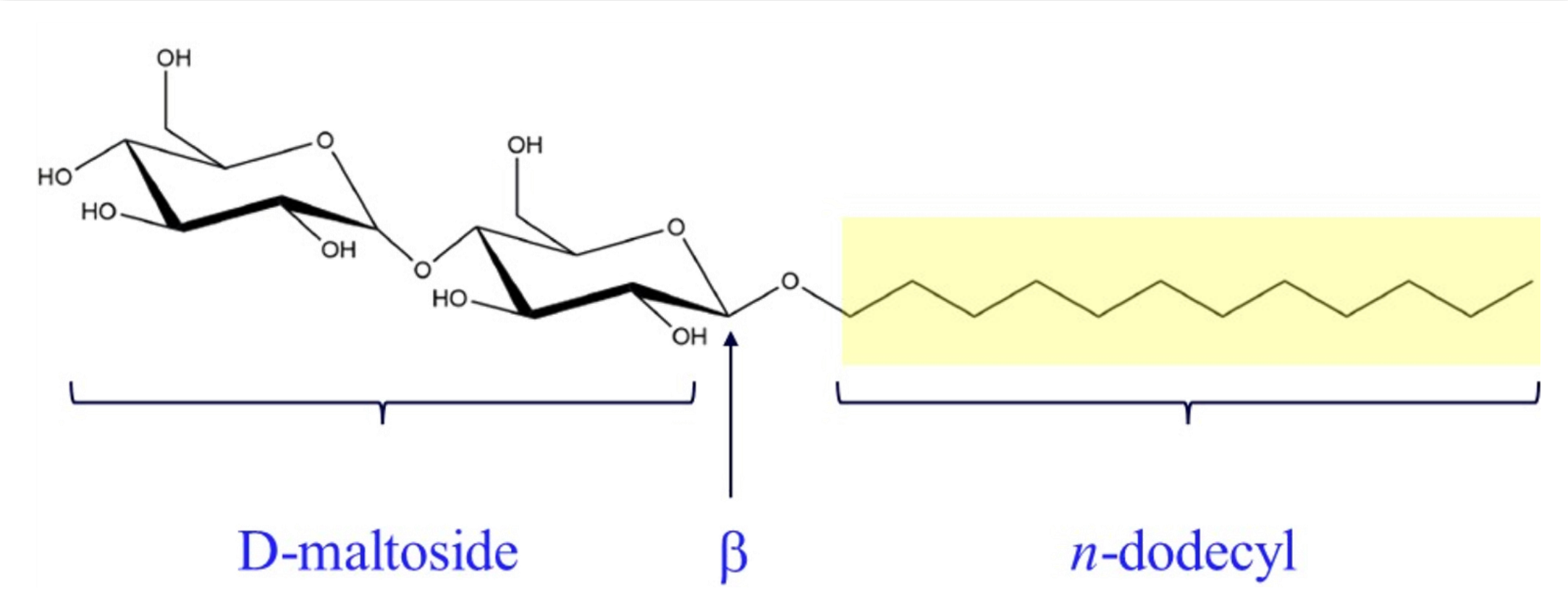
one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any isomers thereof, any esters thereof, and any combinations thereof, in an amount from 30% to 95% (w/w);

one or more alcohols in an amount from 10% to 70% (w/w), wherein the one or more alcohols comprises benzyl alcohol; and

n-dodecyl beta-D-maltoside.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Structure of *n*-dodecyl β-D-maltoside

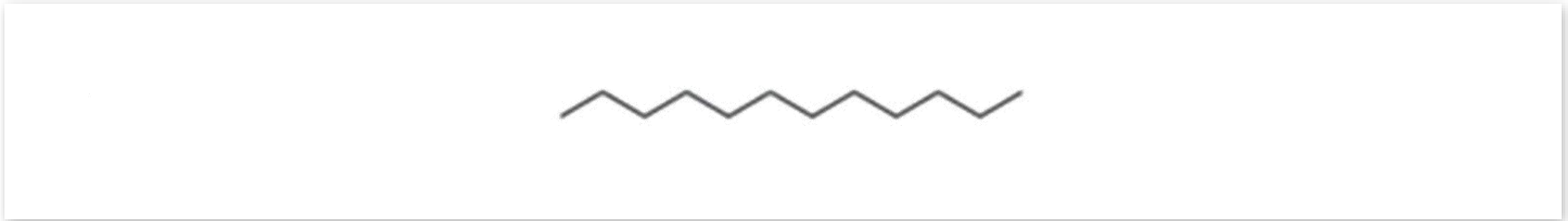


IPR2025-00465, Paper 28 (POR) at 18, EX2073 ¶ 81.

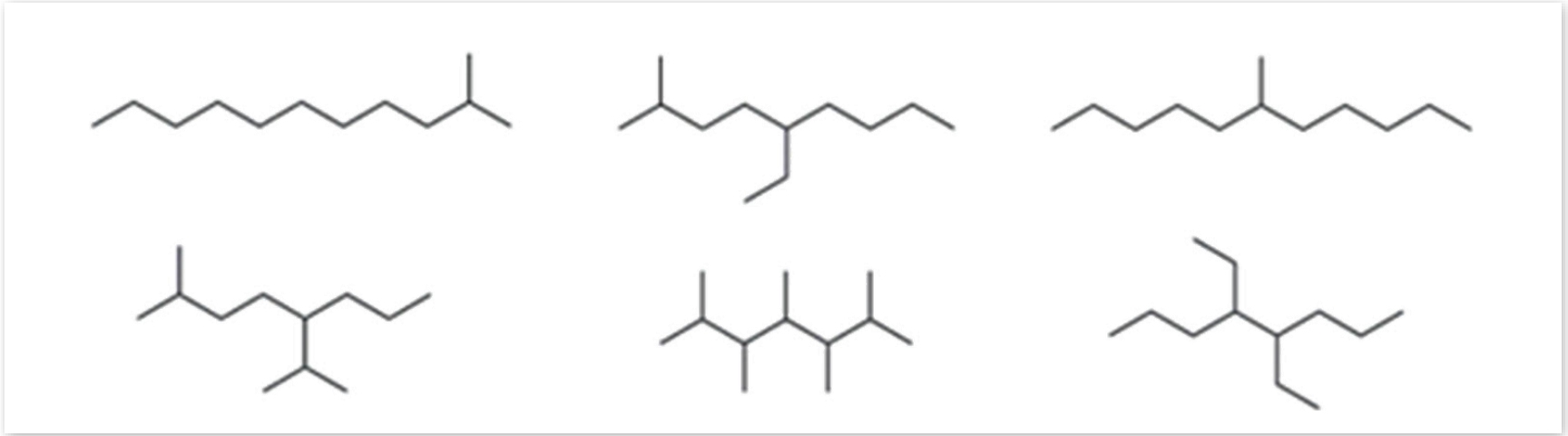
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Linear vs. Branched

Linear



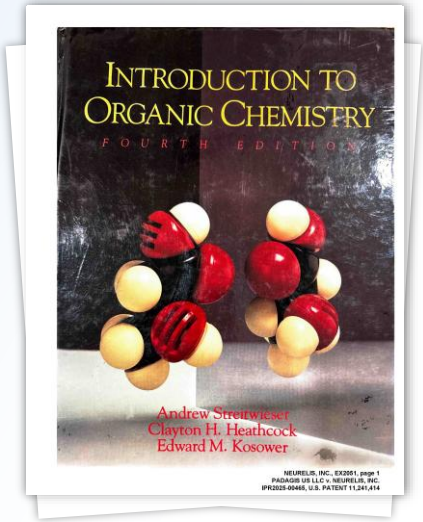
Branched



IPR2025-00465, Paper 28 (POR) at 15, EX2073 ¶¶ 71-72.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

n-alkanes



Streitwieser EX2051

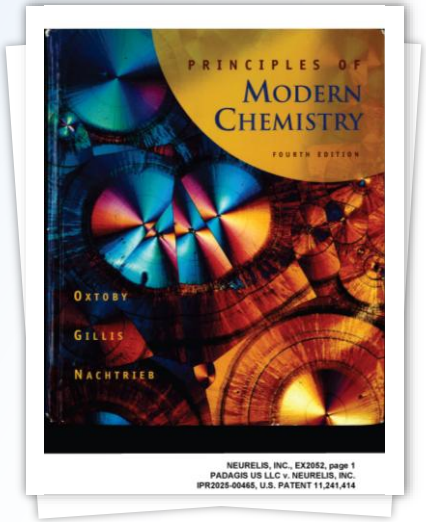
3.5 *n*-Alkanes, the Simplest Organic Compounds

The straight-chain alkanes constitute a family of hydrocarbons in which a chain of CH_2 groups is terminated at both ends by a hydrogen. They have the general formula $H(CH_2)_nH$ or C_nH_{2n+2}. Such a family of compounds, which differ from each other by the number of CH_2 groups in the chain, is called a **homologous series.** The individual members of the family are known as **homologs** of one another. Straight-chain alkanes are called **normal alkanes,** or simply ***n*-alkanes,** to distinguish them from the branched alkanes, which we shall study later.

EX2051 at 9

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

n-alkanes



Oxtoby
EX2052

Petroleum Distillation and the Normal Alkanes

Although crude petroleum contains small amounts of oxygen, nitrogen, and sulfur, its major constituents are **hydrocarbons,** compounds of carbon and hydrogen. The most prevalent hydrocarbons in petroleum are the **straight-chain alkanes** (also called normal alkanes, or *n*-alkanes), which consist of chains of carbon atoms bonded to one another by single bonds, with enough hydrogen atoms on each carbon atom to bring it to the maximum bonding capacity of four. These alkanes have the generic formula C_nH_{2n+2}; Table 17.1 lists the names and formulas of the first few. The ends

EX2052 at 8

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

All Limitations Required

"We first must determine whether [challenger] carried its burden to prove that all claimed limitations are disclosed in the prior art. … [W]e consider motivation to combine and reasonable expectation of success ***only if*** all the elements of an invention are found in a combination of prior art references."

PAR Pharm., Inc. v. TWI Pharms., Inc., 773 F.3d 1186, 1194 (Fed. Cir. 2014) (internal citations omitted).

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

37 C.F.R. § 42.104(b)(4)

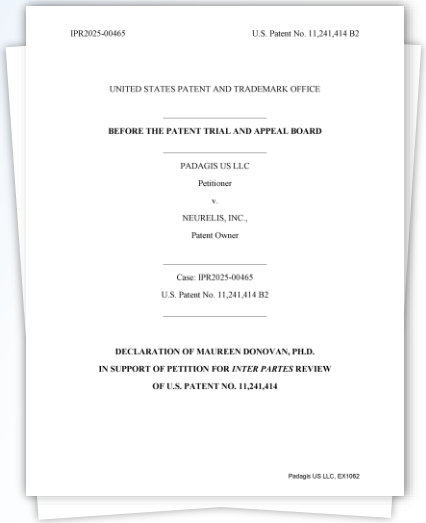


"The petition must specify where each element of the claim is found in the prior art patents or printed publications relied upon."

37 C.F.R. § 42.104(b)(4)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Obviousness of "*n*-dodecyl β-D-maltoside" in Donovan's Declaration


IPR2025-00465 U.S. Patent No. 11,241,414 B2

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PADAGIS US LLC
Petitioner
v.
NEURELIS, INC.,
Patent Owner

Case: IPR2025-00465
U.S. Patent No. 11,241,414 B2

DECLARATION OF MAUREEN DONOVAN, PH.D.
IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 11,241,414

Padagis US LLC, EX1062

Donovan Declaration EX1062

108. Thus, a POSA would be motivated to increase the solubility of diazepam using the Gwozdz solvent system. Given diazepam's potency, and in recognition of its limited water solubility, a POSA would have been motivated to pursue strategies to maximize the solubility of diazepam, and would also look to enhance the permeation of diazepam, based on the teachings of Meezan.

109. For at least these reasons, a POSA would be motivated to add Meezan's alkyl glycosides (e.g., dodecyl maltoside) to Gwozdz's solvent system containing tocopherol, ethanol, and benzyl alcohol that was used to dissolve diazepam.

IPR2025-00465, Paper 48 (Mot. to Strike) at 4-6

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Donovan Testimony

Dr. Donovan

Q. Do you have an understanding of what that "n" prefix means in the context of n-Dodecyl-beta-D-maltoside?

A. It's a structural arrangement indicator that escapes me at the moment.

Q. If I told you it it's an indicator that stands for "normal," would that make sense?

A. Oh, I -- it -- I mean, it makes sense because it's in keeping that I know that what "n" -- I know that's what "n" stands for, but what "normal" is being attributed to is where I -- I'm not willing to state that I know that clearly right now.

Q. You don't recall what structural information the "n" conveys in n-Dodecyl-beta-D-maltoside; is that correct?

A. Not at this moment to testify to.

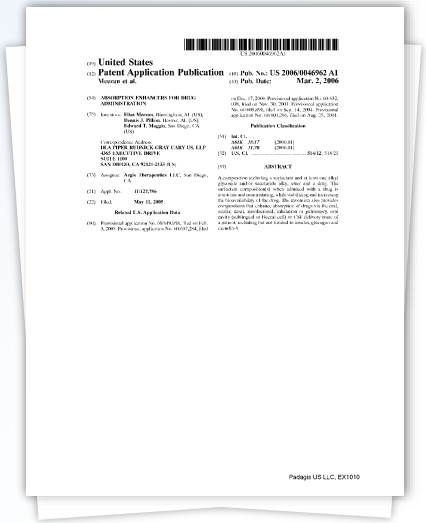
Q. Okay. And that's not an issue you investigated in the course of forming your opinions in this case, correct?

A. Not for a very long time. I probably looked at a description of n-Dodecyl-beta-D-maltoside and noted it, but it didn't stick.

EX2070 at 193:2-25

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Meezan's Disclosure of Alkyl Groups



Meezan EX1010

EXAMPLE 2

Alkyl Glycoside and/or Ester Compositions Stabilize Drugs by Increasing Drug Bioavailability and Reducing Drug Bioavailability Variance

[0149] Stability of the alkyl glycoside depends, in part, on the number of carbon atoms, or branching of the alkyl chain, with tetradecylmaltoside (TDM) having the greatest effect; but other highly branched alkyl chains including DDM also have stabilizing effects. In contrast to Hovgaard-1, which described the preference for a high alkyl glycoside to drug

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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EX1010

92. Regarding the amount of the alkyl glycoside or saccharide alkyl ester to be utilized in the compositions, Meezan states:

> EXAMPLE 2
>
> Alkyl Glycoside and/or Ester Compositions Stabilize Drugs by Increasing Drug Bioavailability and Reducing Drug Bioavailability Variance
>
> Stability of the alkyl glycoside depends, in part, on the number of carbon atoms, or branching of the alkyl chain, with tetradecylmaltoside (TDM) having the greatest effect; but other highly branched alkyl chains including DDM also have stabilizing effects…For example, alkyl glycosides in the range of about 0.01% to about 6% by weight result in good stabilization of the drug…Even more interesting, alkyl glycosides of the invention in the range of about 0.01% to about 6% have increased bioavailability (see FIG. 1).

IPR2025-00465, EX1062 at 47-48

IPR2025-00465, Paper 28 (POR) at 4, 59–64

Meezan's Disclosure of Alkyl Groups

EXAMPLE 2

Alkyl Glycoside and/or Ester Compositions Stabilize Drugs by Increasing Drug Bioavailability and Reducing Drug Bioavailability Variance

[0149] Stability of the alkyl glycoside depends, in part, on the number of carbon atoms, or branching of the alkyl chain, with tetradecylmaltoside (TDM) having the greatest effect; but other highly branched alkyl chains including DDM also have stabilizing effects. In contrast to Hovgaard-1, which described the preference for a high alkyl glycoside to drug

EX1010

Dr. Donovan

Q. Paragraph 149 describes that the DDM it discloses has highly branched alkyl chains, correct? . . . And the DDM it describes in Meezan it describes as having highly branched alkyl chains, correct?

. . .

A. Yes, in this example

Q. Okay. Are you aware of any other example in the patent application that discloses anything specific about the structure of the alkyl chain of the DDM or the TDM or any other alkyl chain?

. . .

A. I could... let's see. I did not put that to memory, so I'd have to look at the other examples to make sure of that

Q. Sitting here right now, you're unaware of any such disclosure?

A. That's correct.

EX2070 (Donovan Dep.) at 119:15–120:22

IPR2025-00465, Paper 28 (POR) at 42–43

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

New Exhibits in Reply

"The Board did not err in refusing the reply brief as improper under 37 C.F.R. § 42.23(b) because IBS relied on an entirely new rationale."

A "new theory of invalidity by reference to new evidence, citing 'a number of non-patent literature references which were not relied upon to support unpatentability in the Petition.'"

Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd., 821 F.3d 1359, 1369 (2016)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

IUPAC


UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PADAGIS US LLC,

Petitioner,

v.

NEURELIS, INC.,

Patent Owner.

Case No. IPR2025-00465
U.S. Patent No. 11,241,414

REPLY DECLARATION OF MAUREEN DONOVAN, PH.D. IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 11,241,414

PAGE 1

Padagis US LLC, EX1078

Donovan Reply Decl. EX1078

18. In fact, IUPAC has long-published several books with chemical nomenclature rules and recommendations. One of those books is referred to as the Blue Book, which promulgates rules for nomenclature of organic compounds, including alkanes. A POSA would have understood that the IUPAC's Blue Book does not recommend the use of the "n-" prefix when naming straight-chain alkanes or alkyl groups. *See, e.g.*, Ex. 1079 (IUPAC 1993) at 4-6.

IPR2025-00465, EX1078 (Donovan Reply Decl.)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

IUPAC

R-2 Parent Hydrides[18] and their Derived Substituent Groups

R-2.0 INTRODUCTION

A 'parent hydride' (see R-0.2.1.1) is the structure which is named before the addition of affixes denoting substituents to yield the name of a specific compound. Its name is understood to signify a definite population of hydrogen atoms attached to a skeletal structure. Acyclic parent hydrides are always unbranched, for example pentane and trisilane; although a few trivial names for branched acyclic hydrocarbons are retained (see R-9.1, Table 19(a), p. 163), their use for naming substitutive derivatives is not recommended. Cyclic parent hydrides are usually either fully saturated, for example, cyclopentane, cyclotrisiloxane, azepane, bicyclo[2.2.2]octane, and spiro[4.5]decane, or fully unsaturated, i.e., they contain the maximum number of noncumulative double bonds, for example, pyridine, 1,3-oxazole, 1*H*-phenalene, phenanthroline, and benzo[*a*]-anthracene. Also, there are parent hydrides that are partially saturated, for example, 1,4-dihydro-1,4-ethanoanthracene and spiro[1,3-dioxolane-2,1′-[1*H*]indene], and that are combinations of cyclic and saturated acyclic structures having retained trivial names (see R-9.1, Table 19(a), p. 163).

R-2.1 MONONUCLEAR HYDRIDES

The names of mononuclear hydrides of the elements for use as parents in substitutive nomenclature are given in Table 2. Many are formed systematically by combining the 'a' term of the element (with elision of the terminal 'a') with the ending '-ane', for example, borane for BH_3, silane for SiH_4, etc. There are important exceptions: methane for CH_4, oxidane for OH_2, sulfane for SH_2, selane for SeH_2, etc., (see Table 2). The systematic alternatives to well established common names, e.g., azane for ammonia, oxidane for water, and chlorane, bromane, etc., for hydrogen chloride, bromide, etc., are necessary for naming some derivatives and for generating names of polynuclear homologues. If the bonding number of the element differs from the normal one as defined in R-1.1, the name of the hydride is modified by affixing a λ^n symbol as instructed by R-1.1.

R-2.2 ACYCLIC POLYNUCLEAR HYDRIDES

R-2.2.1 **Hydrocarbons**

The saturated unbranched acyclic hydrocarbons from C_2 to C_4 are named ethane, propane, and butane (see R-9.1, Table 19(a), p. 162). Systematic names of the higher members of this series consist of a numerical term (see Table 11, p. 71), followed by '-ane' with elision of a terminal 'a' from the basic numerical term. The generic name for saturated acyclic hydrocarbons (branched or unbranched) is 'alkane'. The chain is numbered from one end to the other with arabic numerals.

[18] More detailed recommendations for naming these compounds are given in Sections A, B, and D of the 1979 edition of the IUPAC *Nomenclature of Organic Chemistry*[1].

Table 2 Mononuclear hydrides

BH_3	Borane[a]	OH_2	Oxidane[c,e,f]
CH_4	Methane[b] (Carbane)	SH_2	Sulfane[e,f]
SiH_4	Silane	SH_4	λ^4-Sulfane[e,g]
GeH_4	Germane	SH_6	λ^6-Sulfane[e,g]
SnH_4	Stannane	SeH_2	Selane[e,f,g]
PbH_4	Plumbane	TeH_2	Tellane[e,f]
NH_3	Azane[e,f]	PoH_2	Polane[e,f]
PH_3	Phosphane[b] (Phosphine)	FH	Fluorane[e,f]
PH_5	λ^5-Phosphane[b] (Phosphorane)	ClH	Chlorane[e,f]
AsH_3	Arsane[b] (Arsine)	BrH	Bromane[e,f]
AsH_5	λ^5-Arsane[b] (Arsorane)	IH	Iodane[e,f]
SbH_3	Stibane[b] (Stibine)	IH_3	λ^3-Iodane[h]
SbH_5	λ^5-Stibane[b] (Stiborane)	IH_5	λ^5-Iodane[g]
BiH_3	Bismuthane[b,c] (Bismuthine)	AtH	Astatane[f]

[a] Although analogous names have been suggested for aluminium and gallium hydrides, they are not included in these recommendations.
[b] Preferred name.
[c] 'Ammonia', 'water', 'hydrogen chloride' (and analogues) are common names for NH_3, OH_2, and ClH (and analogues), respectively.
[d] The name amine is used, for example, in *Beilstein*, as a parent hydride name for NH_3.
[e] Exceptions. The expected names, bismane, oxane, thiane, selenane, tellurane and polonane are Hantzsch–Widman names for heteromonocyclic rings (see R-2.3.3).
[f] The normal formulae H_2O, H_2S, etc., have been reversed in this table for the purpose of comparison.
[g] The names 'sulfurane' and 'selenurane', and related names, such as persulfurane and periodinane, which have been used in recent literature, are not recommended.
[h] The name 'iodinane', which has been used in recent literature, cannot be used because it is a Hantzsch–Widman name for a heteromonocyclic iodine ring (see R-2.3.3).

Examples:

$CH_3-CH_2-CH_2-CH_2-CH_2-CH_2-CH_3$ (7 6 5 4 3 2 1)
Heptane

$CH_3-[CH_2]_{58}-CH_3$ (60 1)
Hexacontane

$CH_3-[CH_2]_{21}-CH_3$ (23 1)
Tricosane

R-2.2.2 **Homogeneous hydrides other than hydrocarbons or boron hydrides**[19]

A compound consisting of an unbranched chain containing several identical hetero-atoms saturated with hydrogen atoms, may be named by citing the appropriate multiplying prefix (with *no elision* of the terminal vowel of the multiplying prefix) followed by the appropriate name of the hydride according to R-2.1. If necessary, a λ^n symbol is used, according to R-1.1.

[19] Polyboranes are not covered in these recommendations; because of their unique bonding characteristics, they have been treated in IUPAC *Nomenclature of Inorganic Chemistry*[3], Recommendations I-11.1 through I-11.3, pp. 207–225.

Table 11 Basic numerical terms (multiplying affixes)[51]

Number	Numerical term	Number	Numerical term	Number	Numerical term	Number	Numerical term
1	mono-[a]	11	undeca-	100	hecta-	1000	kilia-
2	di-[c]	12	dodeca-[b]	200	dicta-	2000	dilia-
3	tri-	20	icosa-[c]	300	tricta-	3000	trilia-
4	tetra-	30	triaconta-	400	tetracta-	4000	tetralia-
5	penta-	40	tetraconta-	500	pentacta-	5000	pentalia-
6	hexa-	50	pentaconta-	600	hexacta-	6000	hexalia-
7	hepta-	60	hexaconta-	700	heptacta-	7000	heptalia-
8	octa-	70	heptaconta-	800	octacta-	8000	octalia-
9	nona-	80	octaconta-	900	nonacta-	9000	nonalia-
10	deca-	90	nonaconta-				

[a] When alone, the numerical term for the number 1 is 'mono-' and that for 2 is 'di-'. In association with other numerical terms, the number 1 is represented by 'hen-' (except in the case of 'undeca-') and the number 2 by 'do-' (except in the cases of 'dicta-' and 'dilia-'). The numerical term for the number 11 is 'undeca-'. Compare *mono*chloro with *hen*icosane for the number 21 and *di*chloro with *do*cosane for the number 22.
[b] After 'dodeca-' (12), composite numerical terms are formed systematically by citing the basic terms in the order opposite to that of the constituent arabic numerals. For example, the numerical term for the number 468 is 'octahexacontatetracta-'.
[c] Chemical Abstracts Service and *Beilstein* use eicosa instead of icosa.

The basic numerical terms (multiplying affixes) given in Table 11 are used by direct joining without hyphen.

Numerical terms for use as multiplying prefixes for complex entities, such as substituted substituents, are obtained by adding the ending '-kis' to the numerical term defined as above. However, the ending '-kis' is not used with 'mono-'. As exceptions, 'bis-' is used for the number 2 and 'tris-' for 3.

Examples:

4 tetrakis-
231 hentriacontadictakis-

The following multiplying prefixes are used in names for unbranched assemblies of three or more identical repeating units.

2	bi-	5	quinque-	8	octi-
3	ter-	6	sexi-	9	novi-
4	quater-	7	septi-	10	deci-

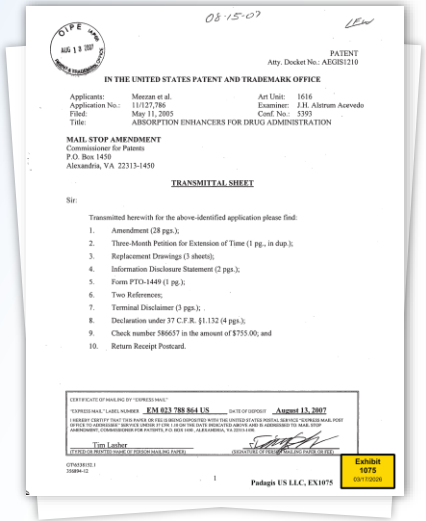
When a substituent is itself substituted (a complex substituent, see R-4.2.4), all the subsidiary substituents are named as prefixes. The substituent bearing the subsidiary substituents is regarded as a 'parent substituent' (analogous to a parent hydride). The nomenclature of the whole substituent is subject to all the procedures adopted for

[51] International Union of Pure and Applied Chemistry. Organic Chemistry Division. Commission on Nomenclature of Organic Chemistry, 'Extension of Rules A-1.1 and A-2.5 Concerning Numerical Terms Used in Organic Nomenclature (Recommendations 1986)', *Pure Appl. Chem.*, **58**, 1693–1696 (1986).

EX1079 at 4–6

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Prosecution History of Meezan



08-15-07 LEW

PATENT
Atty. Docket No.: ADGBS1210

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Meezan et al. Art Unit: 1616
Application No.: 11/127,786 Examiner: J.H. Alstrum Acevedo
Filed: May 11, 2005 Conf. No.: 5393
Title: ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL SHEET

Sir:

Transmitted herewith for the above-identified application please find:

1. Amendment (28 pgs.);
2. Three-Month Petition for Extension of Time (1 pg., in dup.);
3. Replacement Drawings (3 sheets);
4. Information Disclosure Statement (2 pgs.);
5. Form PTO-1449 (1 pg.);
6. Two References;
7. Terminal Disclaimer (3 pgs.);
8. Declaration under 37 C.F.R. §1.132 (4 pgs.);
9. Check number 586657 in the amount of $755.00; and
10. Return Receipt Postcard.

CERTIFICATE OF MAILING BY "EXPRESS MAIL"
"EXPRESS MAIL" LABEL NUMBER EM 023 788 864 US DATE OF DEPOSIT August 13, 2007
I HEREBY CERTIFY THAT THIS PAPER OR FEE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE UNDER 37 CFR 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO MAIL STOP AMENDMENT, COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450
Tim Lasher
(TYPED OR PRINTED NAME OF PERSON MAILING PAPER) (SIGNATURE OF PERSON MAILING PAPER OR FEE)

Exhibit 1075 03/17/2020

GT9433032.1
350894-12

Padagis US LLC, EX1075

EX1075

Please replace paragraph [0117] of the specification with the following amended paragraph:

[0117] Stability of the alkyl glycoside depends, in part, on the number of carbon atoms, or ~~branching~~ length of the alkyl chain, with tetradecylmaltoside (TDM) having the greatest effect; but other ~~highly branched~~ long alkyl chains including DDM also have stabilizing effects. In contrast to Hovgaard-1, which described the preference for a high alkyl glycoside to drug ratio, the instant invention shows that this ratio is much lower. For example, alkyl glycosides in the range of about 0.01% to about 6% by weight result in good stabilization of the drug; whereas Hovgaard-1 shows stabilization is only achieved at much higher ratios of alkyl glycosides to drug (10:1 and 16:1). Even more interesting, alkyl glycosides of the invention in the range of about 0.01% to about 6% have increased bioavailability (see FIG. 1). This is in sharp contrast to Hovgaard-2, which showed relatively low bioavailability (0.5-1%) at the high alkyl glycoside ratios (10:1 and 16:1).

EX1075 at 6

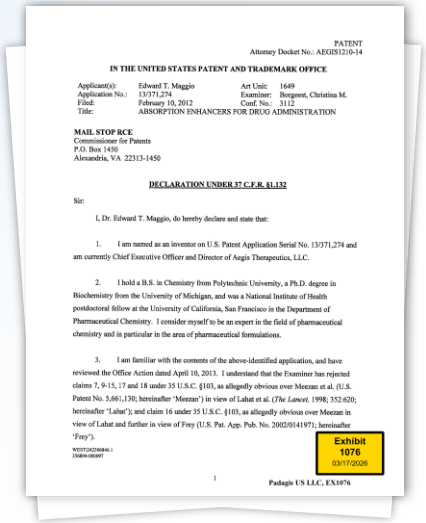
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

"[T]here is no sufficient indication on this record to establish a reasonable likelihood that the [challenged exhibits] are available prior art for an inter partes review, as they are not part of the patent."

Apple Inc., v. DoDots Licensing Solutions LLC, IPR2023-00939, Paper 12 at 15–17 (P.T.A.B. Jan. 3, 2024)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Maggio Declaration



Maggio Decl.
EX1076

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Edward T. Maggio	Art Unit:	1649
Application No.:	13/371,274	Examiner:	Borgeest, Christina M.
Filed:	February 10, 2012	Conf. No.:	3112
Title:	ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION		

MAIL STOP RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132

Date: 19Sept2013

Edward T. Maggio, Ph.D.

EX1076 at 1,3

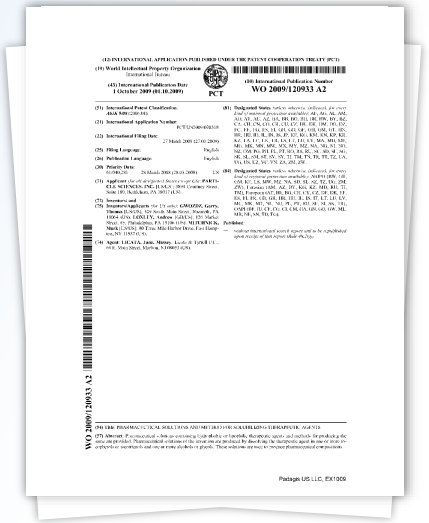
IPR2025-00465, Paper 53 (Sur-Reply) at 18–19

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Non-Obviousness: No Reason to Modify Gwozdz-PCT

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Gwozdz-PCT Does Not Identify Any Deficiencies



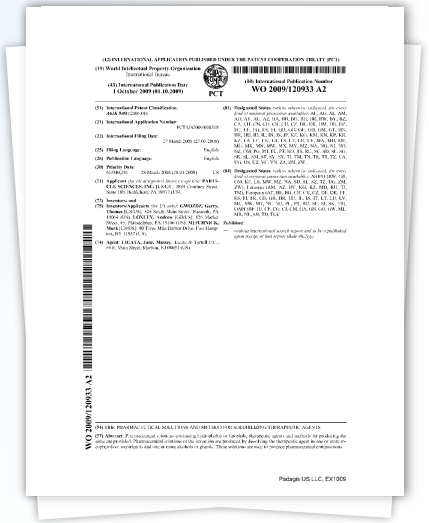
Gwozdz-PCT
EX1009

that is amenable to application to a mucosal membrane. Use of a pharmaceutical solution of the present invention, however, provides for improved ability to dissolve hydrophilic and lipophilic therapeutic agents, thus providing a useful delivery system for administration of such agents to one or more mucosal membranes, including the nasal mucosal membranes. Such solutions can be administered

EX1009 at 9:28-34

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

No Reason to Modify Gwozdz-PCT



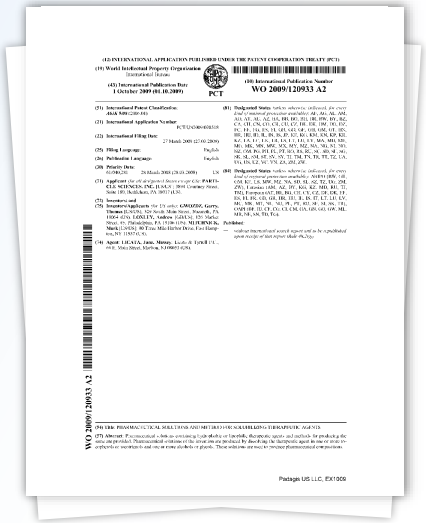
Gwozdz-PCT
EX1009

an emulsion or vesicle, and can be used directly in the production of pharmaceutical compositions. Moreover, the combination of a tocopherol and/or a tocotrienol and an alcohol and/or glycol is much less irritating to the skin and/or mucous membranes than pure alcohol solutions and generally provides higher loading of a therapeutic agent than emulsions, liposomes, encapsulations, or cyclodextrins.

EX1009 at 5:1–7

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Gwozdz-PCT Does Not Identify Any Deficiencies



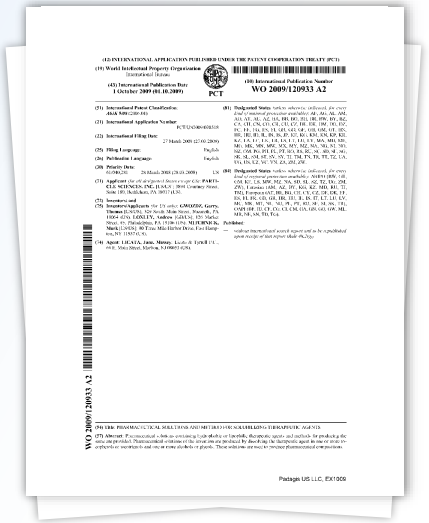
Gwozdz-PCT
EX1009

Pharmaceutical solutions of the instant invention are particularly useful in formulations to be administered to mucosal membranes, i.e. the nasal mucosa or lungs of a subject by any suitable means. For many therapeutic agents, administration via the nasal route provides for faster attainment of therapeutic levels of the therapeutic agent systemically. However, many therapeutic agents are so

EX1009 at 9:19–25

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Gwozdz-PCT Does Not Identify Any Deficiencies



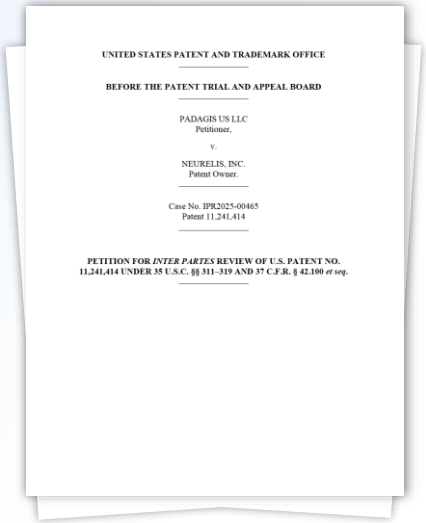
Gwozdz-PCT
EX1009

In accordance with the present invention, solutions of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols are used in the solubilization of hydrophobic or lipophilic therapeutic agents thereby providing increased bioavailability of the therapeutic agent. In some embodiments, the tocopherol(s) and/or tocotrienol(s) is in an amount from about 30% to about 99% (w/w) and the alcohol(s) and/or glycol(s) is in an amount about 1% to about 70% (w/w).

EX1009 at 7:3–11

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Gwozdz-PCT Does Not Identify Any Deficiencies



UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PADAGIS US LLC
Petitioner,

v.

NEURELIS, INC.
Patent Owner.

Case No. IPR2025-00465
Patent 11,241,414

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 11,241,414 UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. § 42.100 *et seq.*

IPR Petition Paper 2

EX1027, p. 354. It was well-known that benzodiazepines have sufficient lipophilic character to readily cross biologic membranes (*id.*), meaning that a POSA would consider benzodiazepine drug compounds to be a logical choice for intranasal administration. *See* EX1062, ¶64.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE



"Board does not explain why a person of skill in the art would conclude that [the primary reference] needed to be modified."

In re Anova Hearing Labs, Inc., 809 Fed. App'x 840, 843 (Fed. Cir. 2020)



"Adding a redundant feature does not constitute a reason to combine."

Ex Parte Tsai-Ching Lu, et al., Appeal 2022-000521, 2022 WL 4957922, at *3 (P.T.A.B. Sept. 30, 2022)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE



"[O]bviousness concerns whether a skilled artisan not only could have made ***but would have*** been motivated to make the combinations or modifications of prior art to arrive at the claimed invention."

Virtek Vision Int'l ULC v. Assembly Guidance Sys., Inc., 97 F.4th 882, 886-87 (Fed. Cir. 2024)



"The obviousness inquiry does not merely ask whether a skilled artisan could combine the references, but instead asks whether 'they would have been motivated to do so.'"

Adidas AG v. Nike, Inc., 963 F.3d 1355, 1359 (Fed. Cir. 2020)

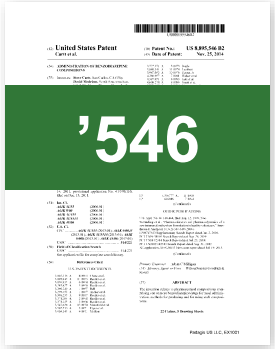
IPR2025-00465, Paper 28 (POR) at 49, 56–58

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Non-Obviousness: Effect of Other Excipients

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ethanol



What is claimed is:

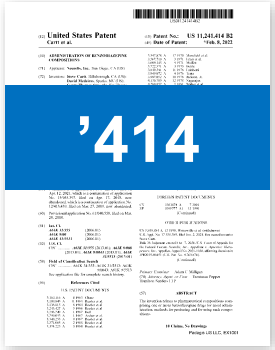
1. A pharmaceutical solution for nasal administration consisting of:

(a) a benzodiazepine drug;

(b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w);

(c) ethanol and benzyl alcohol in a combined amount from about 10% to about 70% (w/w); and

(d) an alkyl glycoside.



What is claimed is:

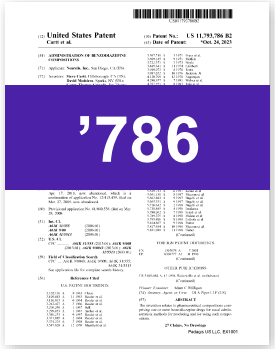
1. A pharmaceutical solution for nasal administration consisting of:

diazepam or a pharmaceutically acceptable salt thereof;

one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from 30% to 95% (w/w);

ethanol and benzyl alcohol in a combined amount from 10% to 70% (w/w); and

n-dodecyl beta-D-maltoside.



What is claimed is:

1. A pharmaceutical solution for nasal administration consisting of:

a therapeutically effective amount of diazepam or a pharmaceutically acceptable salt thereof;

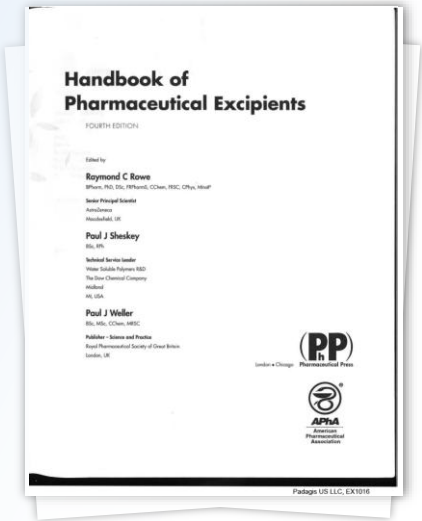
one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any isomers thereof, any esters thereof, and any combinations thereof, in an amount from 30% to 95% (w/w);

one or more alcohols in an amount from 10% to 70% (w/w), wherein the one or more alcohols comprises benzyl alcohol; and

n-dodecyl beta-D-maltoside.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ethanol Deactivation



Rowe
EX1016

Alcohol

1 Nonproprietary Names

BP: Ethanol (96%)
JP: Ethanol
PhEur: Ethanolum (96 per centum)
USP: Alcohol

10 Typical Properties

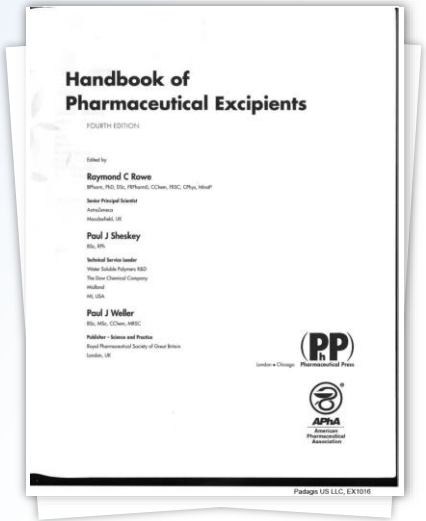
Antimicrobial activity: ethanol is bactericidal in aqueous mixtures at concentrations between 60% and 95% v/v; the optimum concentration is generally considered to be 70% v/v. Antimicrobial activity is enhanced in the presence of edetic acid or edetate salts.[1] Ethanol is inactivated in the presence of nonionic surfactants and is ineffective against bacterial spores.

EX1016 at 13-14

IPR2025-00465, Paper 28 (POR) at 50–51

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Skin Penetrant



Rowe
EX1016

Alcohol

1 Nonproprietary Names

BP: Ethanol (96%)
JP: Ethanol
PhEur: Ethanolum (96 per centum)
USP: Alcohol

6 Functional Category

Antimicrobial preservative; disinfectant; skin penetrant; solvent.

EX1016 at 13

IPR2025-00465, Paper 28 (POR) at 50–51

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Dr. Donovan Testimony:

Dr. Donovan

Q. What is the third of the functions that Rowe discloses ethanol possesses?

…

A. Third category: "Skin Penetrant."

Q. That's another word of saying an absorption enhancer, right?

A. Yes.

EX2070 at 169:21–170:4

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

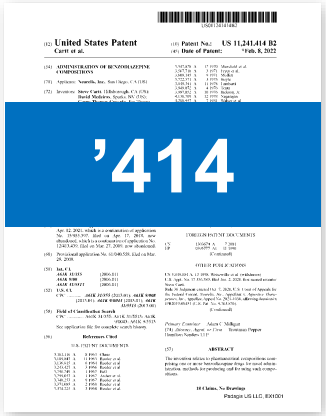


"Adding a redundant feature does not constitute a reason to combine."

Ex Parte Tsai-Ching Lu, et al., Appeal 2022-000521, 2022 WL 4957922, at *3 (P.T.A.B. Sept. 30, 2022)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Tocopherols



What is claimed is:

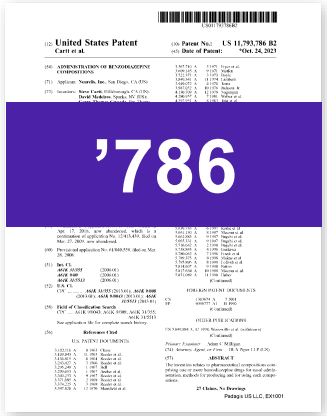
1. A pharmaceutical solution for nasal administration consisting of:

diazepam or a pharmaceutically acceptable salt thereof;

one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from 30% to 95% (w/w);

ethanol and benzyl alcohol in a combined amount from 10% to 70% (w/w); and

n-dodecyl beta-D-maltoside.



What is claimed is:

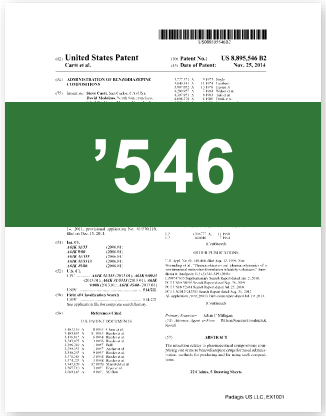
1. A pharmaceutical solution for nasal administration consisting of:

a therapeutically effective amount of diazepam or a pharmaceutically acceptable salt thereof;

one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any isomers thereof, any esters thereof, and any combinations thereof, in an amount from 30% to 95% (w/w);

one or more alcohols in an amount from 10% to 70% (w/w), wherein the one or more alcohols comprises benzyl alcohol; and

n-dodecyl beta-D-maltoside.



What is claimed is:

1. A pharmaceutical solution for nasal administration consisting of:

(a) a benzodiazepine drug;

(b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w);

(c) ethanol and benzyl alcohol in a combined amount from about 10% to about 70% (w/w); and

(d) an alkyl glycoside.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Dr. Donovan Testimony:

Dr. Donovan

Q. [O]ne of the reasons for the cautions that are stated here, to preserve in tight containers, to protect from light, to cover with a blanket of inert gas, was a concern that Vitamin E might oxidize; is that right?

A. Oftentimes, those same instructions are provided for materials that oxidize.

Q. And is that a form of degradation?

A. I -- yeah, I believe that would be a generally-accepted definition. It's a chemical change in the substance and -- and, yeah, we -- in pharmaceuticals, we usually refer to those as "degradants.

EX2070 at 284:1–13

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Non-Obviousness: Motivation to Combine with Meezan

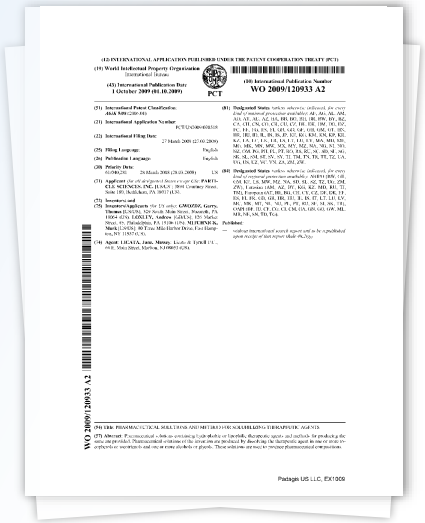
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

"[P]rior art must be considered for all its teachings, not selectively"

Henny Penny Corp. v. Frymaster LLC, 938 F.3d 1324, 1332 (Fed. Cir. 2019)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

The Embodiments of Gwozdz-PCT



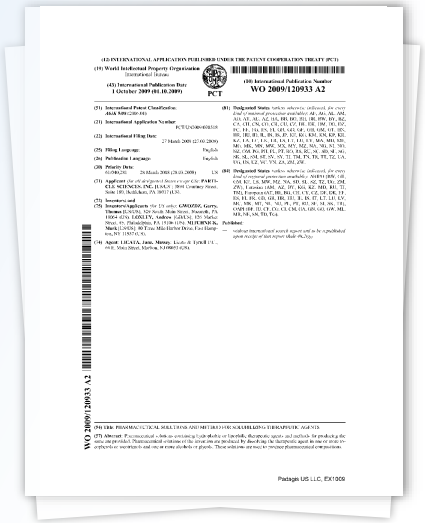
Gwozdz-PCT
EX1009

Pharmaceutical solutions of the invention can be formulated into pharmaceutical compositions for administration to animals, preferably humans, via intravascular, oral, intramuscular, cutaneous and subcutaneous routes. Specifically, pharmaceutical compositions of the present invention can be administered by any of the following nonlimiting exemplary routes, intraabdominal, intraarterial, intraarticular, intracapsular, intracervical, intracranial, intraductal, intradural, intralesional, intralocular, intralumbar, intramural, intranasal, intraocular, intraoperative, intraparietal, intraperitoneal, intrapleural, intrapulmonary, intraspinal, intrathoracic, intratracheal, intratympanic, intrauterine, and intraventricular. The pharmaceutical compositions of the present invention can be nebulized using mechanical nebulizers or suitable aerosol propellants which are known in the art for pulmonary delivery of lipophilic compounds. The most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular therapeutic agent which is being used.

EX1009 (Gwozdz-PCT) at 8:32-9:18

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

The Embodiments of Gwozdz-PCT: Nasal



Gwozdz-PCT
EX1009

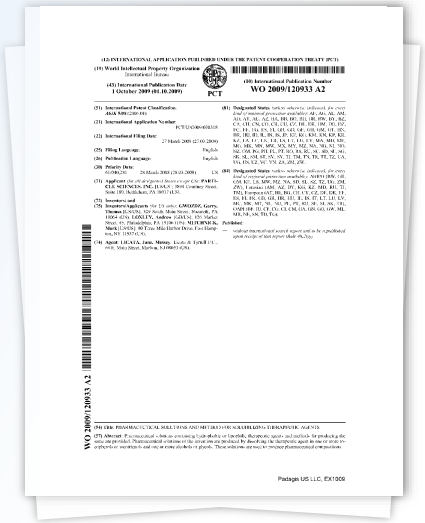
Pharmaceutical solutions of the instant invention are particularly useful in formulations to be administered to mucosal membranes, i.e. the nasal mucosa or lungs of a subject by any suitable means. For many therapeutic agents, administration via the nasal route provides for faster attainment of therapeutic levels of the therapeutic agent systemically. However, many therapeutic agents are so slightly soluble in water that a therapeutically effective amount cannot be dissolved in a volume of aqueous solvent that is amenable to application to a mucosal membrane. Use of a pharmaceutical solution of the present invention, however, provides for improved ability to dissolve hydrophilic and lipophilic therapeutic agents, thus providing a useful delivery system for administration of such agents to one or more mucosal membranes, including the nasal mucosal membranes. Such solutions can be administered via, for example, a metered dose inhaler or nebulizer, or in a mist sprayer.

EX1009 (Gwozdz-PCT) at 9:19–10:2

IPR2025-00465, Paper 28 (POR) at 53–54

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

The Embodiments of Gwozdz-PCT: Injections



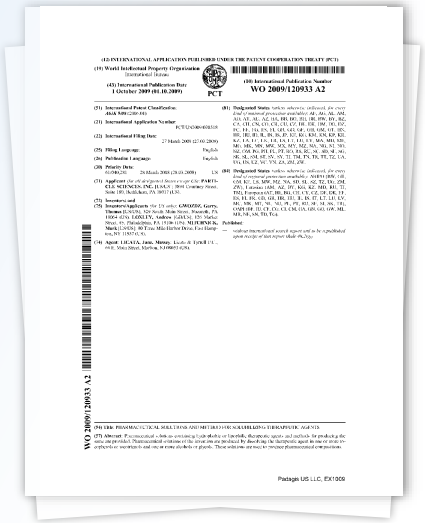
Gwozdz-PCT
EX1009

The instant pharmaceutical solutions comprising a therapeutic agent, one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols can also be formulated into a pharmaceutical composition for injection by combining the instant pharmaceutical solution with, *e.g.*, saline solution or water and a Vitamin E solubilizing agent such as Cremophor. Such pharmaceutical compositions may further contain other pharmaceutically acceptable additives such as, but not limited to, acidifying, alkalizing, buffering, chelating, complexing and solubilizing agents, antioxidants and antimicrobial preservatives, penetration enhancers, humectants, suspending and/or viscosity modifying agents, tonicity and wetting or other biocompatible materials.

EX1009 (Gwozdz-PCT) at 10:3–16

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

The Embodiments of Gwozdz-PCT: Oral



Gwozdz-PCT
EX1009

For oral therapeutic administration, the instant pharmaceutical solutions can be combined with one or more carriers and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums, foods and the like. Such compositions and preparations should contain at least 0.1% of active compound. Tablets, troches, pills, capsules, and the like can also contain one or more of the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. The above listing is merely representative and one skilled in the art could envision other binders, excipients, sweetening agents and the like. When the unit dosage form is a capsule, it can contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials can be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules can be coated with gelatin, wax, shellac or sugar and the like.

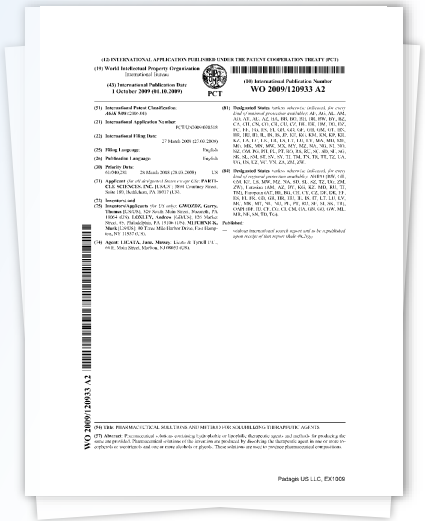
A syrup or elixir can contain the instant pharmaceutical solution, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be substantially non-toxic in the amounts employed.

In addition, the instant pharmaceutical solution can be formulated into sustained-release preparations and devices including, but not limited to, those relying on osmotic pressures to obtain a desired release profile.

EX1009 (Gwozdz-PCT) at 10:17–11:16

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

The Embodiments of Gwozdz-PCT: Parenteral



Gwozdz-PCT
EX1009

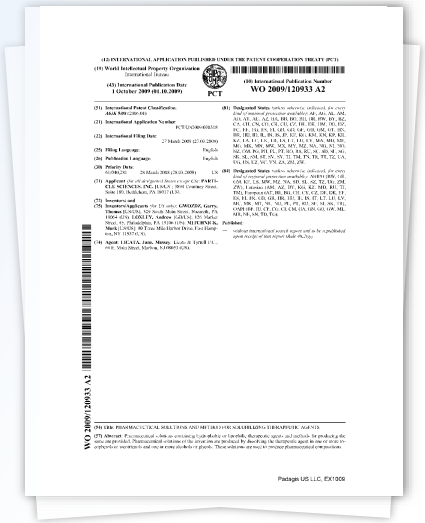
Formulations suitable for parenteral administration can be aqueous or non-aqueous injection solutions, which are generally isotonic with the blood of the intended recipient. These preparations can contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient. Aqueous and non-aqueous sterile suspensions can include suspending agents and thickening agents. The formulations can be presented in unit\dose or multi-dose containers, for example sealed ampoules and vials.

EX1009 (Gwozdz-PCT) at 11:17–26

IPR2025-00465, Paper 28 (POR) at 53–54

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

The Embodiments of Gwozdz-PCT: Topical



Gwozdz-PCT
EX1009

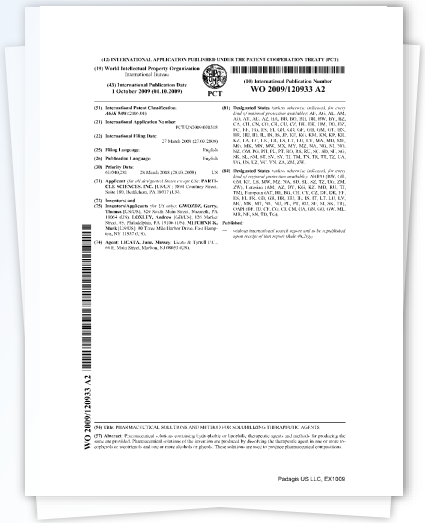
Formulations suitable for topical application to the skin can take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, oil or other pharmaceutical formulation which accomplishes direct contact between the therapeutic agent and the skin. Topical formulations can also be prepared which are suitable for occlusive therapy.

Formulations in the forms of ointments, creams, lotions and pastes can generally have carriers in the forms of oleaginous bases (*e.g.*, White Petrolatum and White Ointment); absorption bases formed by adding a water-in-oil emulsifying agent to an oleaginous base (*e.g.*, Hydrophilic Petrolatum, AQUABASE, and AQUAPHOR); water-in-oil emulsion bases, prepared by adding water to an absorption base (*e.g.*, HYDROCREAM, EUCERIN, NIVEA, and Cold Cream); oil-in-water emulsion bases (*e.g.*, DERMABASE, UNIBASE, VELVACHOL, and hydrophilic ointment); and water soluble bases (*e.g.*, polyethylene glycol ointment such as PEG 400-600 G or PEG 3350-400 G). Suitable carriers to produce a spray, gel, or aerosol are well-known in the art.

EX1009 (Gwozdz-PCT) at 11:27–12:11

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

The Embodiments of Gwozdz-PCT: Transdermal



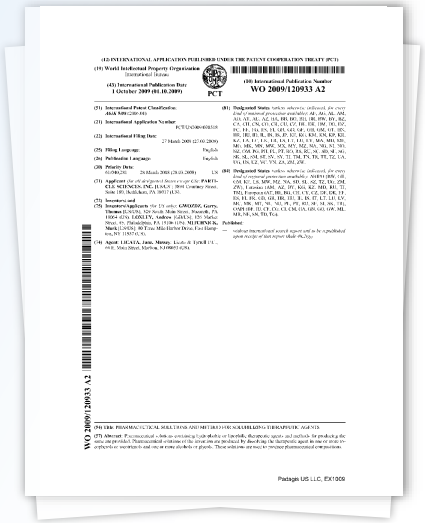
Gwozdz-PCT
EX1009

Formulations suitable for transdermal administration can be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Formulations suitable for transdermal administration can also be delivered by iontophoresis (*see*, for example, *Pharmaceutical Research* 3 (6):318 (1986)) and typically take the form of an optionally buffered aqueous solution. Formulations of the present invention are also suitable for delivery via microneedle delivery technology for cutaneous administration.

EX1009 (Gwozdz-PCT) at 12:28–13:3

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

The Embodiments of Gwozdz-PCT: "other pharmaceutically acceptable additives"



Gwozdz-PCT
EX1009

The instant pharmaceutical solutions comprising a therapeutic agent, one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols can also be formulated into a pharmaceutical composition for injection by combining the instant pharmaceutical solution with, *e.g.*, saline solution or water and a Vitamin E solubilizing agent such as Cremophor. Such pharmaceutical compositions may further contain other pharmaceutically acceptable additives such as, but not limited to, acidifying, alkalizing, buffering, chelating, complexing and solubilizing agents, antioxidants and antimicrobial preservatives, penetration enhancers, humectants, suspending and/or viscosity modifying agents, tonicity and wetting or other biocompatible materials.

EX1009 (Gwozdz-PCT) at 10:3–16

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

New Embodiments in Reply

"[A] reply argument is proper when it responds to the patent owner's arguments or the Board's observations without 'point[ing] to any new embodiments' of a prior art reference not previously identified in the petition."

Corephotonics, Ltd. v. Apple Inc., 84 F.4th 990, 1008-1009 (Fed. Cir. 2023)

"It is not permissible for a reply to include 'previously unidentified portions of a prior-art reference to make a meaningfully distinct contention [and cite] several new non-patent literature references' to support obviousness opinions."

Apple Inc. v. Andrea Elecs. Corp., 949 F.3d 697, 706 (Fed. Cir. 2020)

IPR2025-00465, Paper 48 (Mot. to Strike) at 7-10, Paper 50 (Reply Mot. to Strike) at 4

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Bioavailability

Gwozdz-PCT

Formulations suitable for parenteral administration can be aqueous or non-aqueous injection solutions, which are generally isotonic with the blood of the intended recipient. These preparations can contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient. Aqueous and non-aqueous sterile suspensions can include suspending agents and thickening agents. The formulations can be presented in unit\dose or multi-dose containers, for example sealed ampoules and vials.

EX1009 (Gwozdz-PCT) at 11:17-26

Brown Declaration

F. BIOAVAILABILITY

109. Bioavailability refers to the proportion of an administered drug that reaches the systemic circulation in its active form and is available to exert its therapeutic effect. For a drug to exert its desired therapeutic effect, it must find its way to the location in the body where that effect can manifest. The most direct way to achieve this is to infuse the drug intravenously into the body's systemic blood circulation. This route of administration provides what is usually defined as absolute or 100% bioavailability. IV infusion is complicated by the need to have medical

IPR2025-00465, EX2073 ¶109

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE



"One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art …."

In re Fine, 837 F.2d 1071, 1075 (Fed. Cir. 1998)

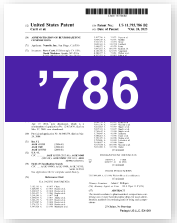


"[W]hether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, in making the combination available"

In re Fulton, 391 F.3d 1195, 1200 (Fed. Cir. 2004)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Diazepam



What is claimed is:

1. A pharmaceutical solution for nasal administration consisting of:

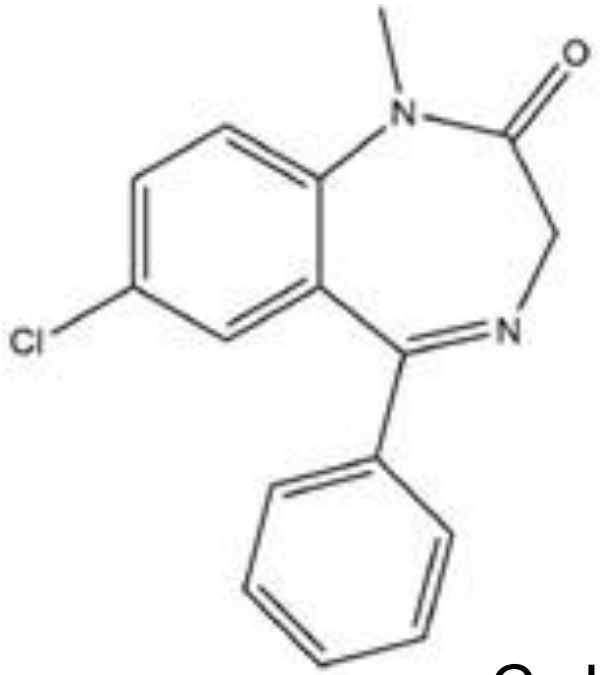
a therapeutically effective amount of diazepam or a pharmaceutically acceptable salt thereof;



What is claimed is:

1. A pharmaceutical solution for nasal administration consisting of:

diazepam or a pharmaceutically acceptable salt thereof;



$C_{16}H_{13}ClN_2O$

285 Daltons

Dr. Donovan

Q. Would you consider diazepam a small molecule?
A. I would consider it a small organic molecule, yes.

EX2070 at 43:22–25

Macromolecules in Meezan

[0130] Therapeutic agents or drugs of the present invention can be peptides or proteins, medically or diagnostically useful, of small to medium size, e.g. up to about 15 kD, 30 kD, 50 kD, 75 kD, etc., or a protein having between about 1-300 amino acids or more. The methods of the invention also anticipate the use of small molecules, for example, an organic compound that has a molecular weight of less than 3 kD, or less than 1.5 kD.

[0131] The mechanisms of improved drug absorption according to the invention are generally applicable and should apply to all such peptides or protein, although the degree to which their absorption is improved may vary according to the molecular weight (MW) and the physicochemical properties of the peptide or protein, and the particular enhancer used. Examples of peptides or protein include vasopressin, vasopressin polypeptide analogs, desmopressin, glucagon, corticotropin (ACTH), gonadotropin, calcitonin, C-peptide of insulin, parathyroid hormone (PTH), growth hormone (HG), human growth hormone (hGH), growth hormone releasing hormone (GHRH), oxytocin, corticotropin releasing hormone (CRH), somatostatin or somatostatin polypeptide analogs, gonadotropin agonist or gonadotrophin agonist polypeptide analogs, human atrial natriuretic peptide (ANP), human thyroxine releasing hormone (TRH), follicle stimulating hormone (FSH), and prolactin.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Macromolecules

Dr. Donovan

Q. And you would agree that none of the examples test the effect of an alkyl glycoside or a saccharide alkyl ester as an absorption enhancer for a small molecule, correct?

A. All of the examples starting on page 13 and beyond I believe are focused on -- (reviewing document) -- either involved studying usual blood glucose decrease after administration of insulin or miacalcin concentration or the concentration of salmon calcitonin, likely.

Q. And both of those compounds, insulin and salmon calcitonin, are not small molecules whatever they might otherwise be, fair?

A. They are not considered to be small molecules

. . .

Q. And when you discussed Exendin and Glucagon, those are also peptides, proteins?

A. Yes, they are peptides.

Q. Okay. Not small molecules?

A. Yes.

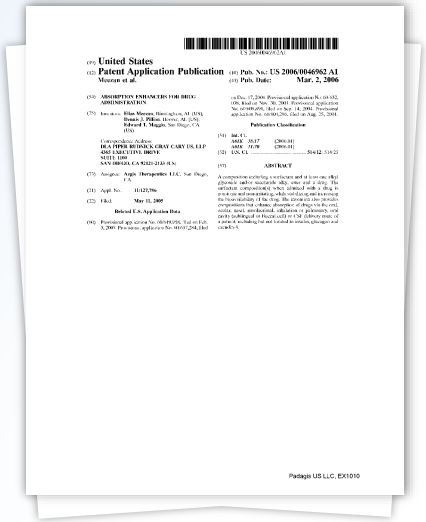
EX2070 at 141:9–142:1, 143:14–18

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Non-Obviousness: Motivation to Select a Dodecyl Maltoside

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Meezan



(19) United States
(12) Patent Application Publication
Meezan et al.
(10) Pub. No.: US 2006/0046962 A1
(43) Pub. Date: Mar. 2, 2006

ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION

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Assignee: Aegis Therapeutics LLC, San Diego, CA

Appl. No.: 11/122,596

Filed: May 11, 2005

Related U.S. Application Data

Publication Classification

ABSTRACT

Padagis US LLC, EX1010

Meezan
EX1010

[0058] As described above, the hydrophobic alkyl can thus be chosen of any desired size, depending on the hydrophobicity desired and the hydrophilicity of the saccharide moiety. For example, one preferred range of alkyl chains is from about 9 to about 24 carbon atoms. An even more preferred range is from about 9 to about 16 or about 14 carbon atoms. Similarly, some preferred glycosides include maltose, sucrose, and glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12, 13, 14, 16, 18, 20, 22, or 24 carbon atoms, e.g., nonyl-, decyl-, dodecyl- and tetradecyl sucroside, glucoside, and maltoside, etc. These compositions are nontoxic, since they are degraded to an alcohol and an oligosaccharide, and amphipathic.

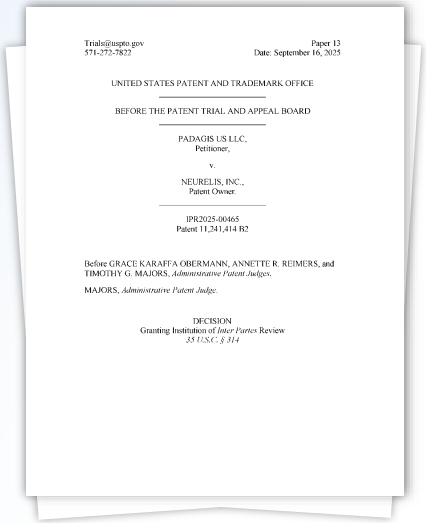
Further, preferred glycosides can include maltose, sucrose, and glucose linked by glycosidic linkage to an alkyl chain of about 9-16 carbon atoms, e.g., nonyl-, decyl-, dodecyl- and tetradecyl sucroside, glucoside, and maltoside. Again, these

EX1010 at ¶ [0061]

IPR2025-00465, Paper 53 (Sur-Reply) at 19–20

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Meezan



Trials@uspto.gov
571-272-7822

Paper 13
Date: September 16, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PADAGIS US LLC,
Petitioner,

v.

NEURELIS, INC.,
Patent Owner.

IPR2025-00465
Patent 11,241,414 B2

Before GRACE KARAFFA OBERMANN, ANNETTE R. REIMERS, and TIMOTHY G. MAJORS, *Administrative Patent Judges*.

MAJORS, *Administrative Patent Judge*.

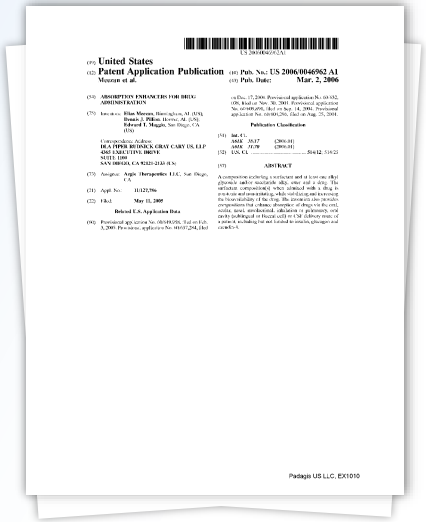
DECISION
Granting Institution of *Inter Partes* Review
35 USC § 314

Institution Decision
Paper 13

According to Meezan, the surfactant of the invention preferably "consists of at least one suitable alkyl glycoside." *Id.* ¶ 54. Meezan discloses that "[a]lkyl glycosides of the present invention can include, but are not limited to: alkyl glycosides, such as octyl-, nonyl-, decyl-, undecyl-, dodecyl-, tridecyl-, . . . and octadecyl-α- or β-D-maltoside, -glucoside or sucroside." *Id.* ¶ 56; *see also id.* ¶¶ 58 (disclosing "preferred glycosides include maltose, sucrose, and glucose linked by a glycosidic linkage to an alkyl chain of 9, 10, 12, 13, 14, 16, 18, 20, 22, or 24 carbon atoms, e.g., nonyl-, decyl-, dodecyl- and tetradecyl sucroside, glucoside, and maltoside, etc."), 61 ("preferred glycosides can include maltose" linked to an "alkyl chain of about 9-16 carbons" such as dodecyl maltoside). In examples, Meezan discloses a use of dodecyl maltoside as the surfactant. *Id.* ¶¶ 153–159 (Example 3 (administration of insulin via ocular route); Table I (eye drops containing insulin and various concentrations of dodecyl maltoside)); *see also id.* ¶ 158 ("The effects of the alkylmaltosides as absorption enhancers are dose-dependent.").

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

No Reason to Modify



Meezan
EX1010

[0157] Several other alkylmaltosides are also effective as absorption enhancers for ocular administration of insulin including 0.5% tridecylmaltoside (see Table III) and 0.125% (Table II) and 0.5% tetradecyl maltoside. These studies show that alkylmaltosides with the longer alkyl chains (or number of carbon atoms), e.g., dodecyl-, tridecyl- and tetradecyl-β-D-maltosides, are more effective. The increase in the number of carbon atoms also contributes to the greater hydrophobic/hydrophilic structural balance and absorption enhancing effect. The shorter alkyl chains (fewer carbon atoms) e.g., decylmaltoside, or no, e.g., octylmaltoside, produce less absorption enhancing activity. It is noted that the most effective alkylmaltosides produce effects comparable to or greater than those seen with other absorption enhancers such as saponin, and with the added advantage that they can be metabolized to nontoxic products following systemic absorption.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

No Reason to Modify

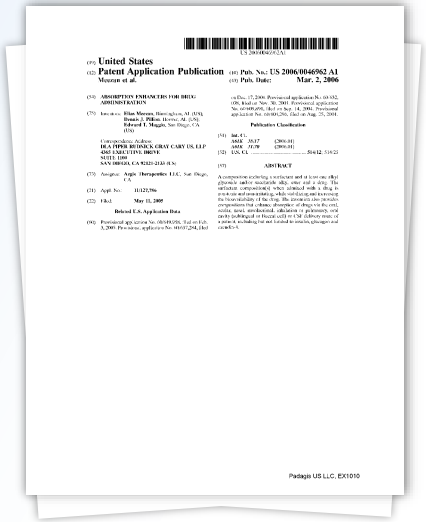


"The mere fact that these possible arrangements existed in the prior art does not provide a reason that a skilled artisan would have [made the combination]"

Virtek Vision Int'l ULC v. Assembly Guidance Sys., Inc., 97 F.4th 882, 887 (Fed. Cir. 2024)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Preference for TDM



(12) United States
(12) Patent Application Publication
Meezan et al.
(10) Pub. No.: US 2006/0046962 A1
(43) Pub. Date: Mar. 2, 2006

(54) ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION

(75) Inventors: Elias Meezan, Birmingham, AL (US); Dennis J. Pillion, Trussville, AL (US); Edward T. Maggio, San Diego, CA (US)

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(73) Assignee: Aegis Therapeutics LLC, San Diego, CA

(21) Appl. No.: 11/122,596

(22) Filed: May 11, 2005

Related U.S. Application Data

(60) Provisional application No. 60/569,926, filed on May 11, 2004. Provisional application No. 60/572,294, filed on May 17, 2004. Provisional application No. 60/601,132, filed on Aug. 13, 2004. Provisional application No. 60/601,129, filed on Aug. 13, 2004. Provisional application No. 60/601,129, filed on Aug. 25, 2004.

Publication Classification

(51) Int. Cl.
A61K 31/7028 (2006.01)
A61K 31/70 (2006.01)
(52) U.S. Cl. 514/22; 514/23

(57) ABSTRACT

A composition including a surfactant and at least one alkyl glycoside and/or ester thereof, and a drug, the drug being a therapeutic compound which, combined with a drug, is poorly soluble and non-irritating, which will dissipate increasing the bioavailability of the drug. The invention also includes compositions that enhance absorption of drugs via the oral, buccal, pulmonary, nasal, ocular, vaginal, rectal, and otic cavity (including soft tissue) and/or CSF. Delivery route of a protein, including but not limited to insulin, glucagon and calcitonin.

Padagis US LLC, EX1010

Meezan
EX1010

EXAMPLE 2

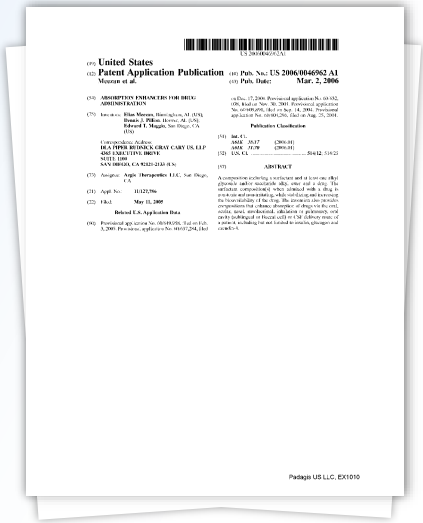
Alkyl Glycoside and/or Ester Compositions Stabilize Drugs by Increasing Drug Bioavailability and Reducing Drug Bioavailability Variance

[0149] Stability of the alkyl glycoside depends, in part, on the number of carbon atoms, or branching of the alkyl chain, with tetradecylmaltoside (TDM) having the greatest effect; but other highly branched alkyl chains including DDM also have stabilizing effects. In contrast to Hovgaard-1, which described the preference for a high alkyl glycoside to drug

[0160] Studies with alkylglucosides were also conducted; 0.5% hexylglucoside and 0.5% heptylglucoside were ineffective at promoting insulin absorption from the eye, but 0.5% nonylglucoside effectively stimulated insulin absorption and reduced blood glucose levels (from 297 mg/dl to 150 mg/dl). This result once further supports that the alkyl chain length, as well as the carbohydrate moiety, play critical roles in effectively enhancing insulin absorption.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Preference for TDM



(19) United States
(12) Patent Application Publication
Meezan et al.
(10) Pub. No.: US 2006/0046962 A1
(43) Pub. Date: Mar. 2, 2006

(54) ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION

(75) Inventors: Elias Meezan, Birmingham, AL (US); Dennis J. Pillion, Irvine, AL (US); Edward T. Maggio, San Diego, CA (US)

Correspondence Address:
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(73) Assignee: Aegis Therapeutics LLC, San Diego, CA

(21) Appl. No.: 11/222,786

(22) Filed: May 11, 2005

Related U.S. Application Data

(60) Provisional application No. 60/569,956, filed on May 11, 2004. Provisional application No. 60/572,294, filed

Publication Classification

(51) Int. Cl.
A61K 38/17 (2006.01)
A61K 31/70 (2006.01)
(52) U.S. Cl. 514/12; 514/23

(57) ABSTRACT

A composition including a surfactant and at least one alkyl glycoside and/or sucrose ester fatty acid, and a therapeutically effective amount of a drug is provided. The surfactant and alkyl glycoside, which, combined with a drug, is non-toxic and non-irritating, which will dramatically increase the bioavailability of the drug. The formulation also includes compositions that enhance absorption of drugs to the oral, buccal, nasal, pulmonary, vaginal, ocular, and rectal mucosa, thereby facilitating the systemic delivery of CNS drugs, drugs of a protein nature, including but not limited to insulin, glucagon and calcitonin.

Padagis US LLC, EX1010

Meezan
EX1010

EXAMPLE 1

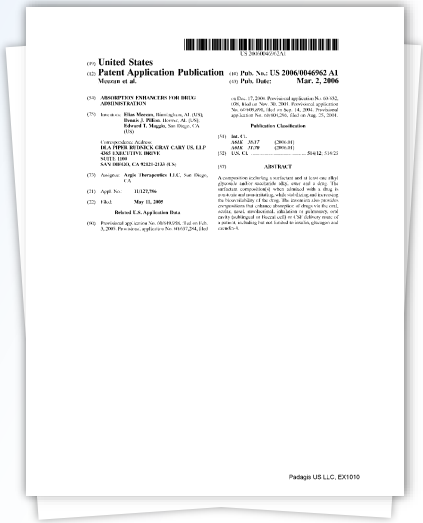
Alkyl Glycoside and/or Sucrose Ester Formulations Do Not Cause Mucosa Irritation or Disruption

[0146] The nasal mucosa is highly vascularized and hence optimal for high drug permeation. Moreover, absorption of drug(s) through the nasal mucosa is available to the central nervous system (CNS). Although local application of drugs is desirable, a challenge for this method of administration is mucosal irritancy.

[0147] A formulation consisting of an alkyl glycoside (0.125% TDM) in a commercial over-the-counter (OTC) nasal saline was administered in vivo to human nasal epithelium over a period of over one month. The 0.125% TDM formulation is compared to the control, namely the same commercial (OTC) nasal saline, over the same period of time. Results show that during and after 33 days of daily TDM administration (i.e., the duration of the study), there is no observable irritation of the nasal mucosa (data not shown). Thus, compositions of the invention are non-toxic and non-irritable providing repeated and long-term intranasal administration, which is beneficial for those patients with chronic and ongoing disease(s).

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Preference for TDM



Meezan
EX1010

EXAMPLE 2

Alkyl Glycoside and/or Ester Compositions Stabilize Drugs by Increasing Drug Bioavailability and Reducing Drug Bioavailability Variance

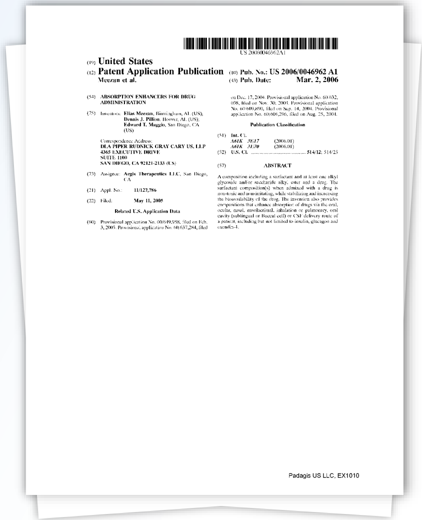
[0149] Stability of the alkyl glycoside depends, in part, on the number of carbon atoms, or branching of the alkyl chain, with tetradecylmaltoside (TDM) having the greatest effect; but other highly branched alkyl chains including DDM also have stabilizing effects. In contrast to Hovgaard-1, which described the preference for a high alkyl glycoside to drug ratio, the instant invention shows that this ratio is much lower. For example, alkyl glycosides in the range of about 0.01% to about 6% by weight result in good stabilization of the drug; whereas Hovgaard-1 shows stabilization is only achieved at much higher ratios of alkyl glycosides to drug (10:1 and 16: 1). Even more interesting, alkyl glycosides of the invention in the range of about 0.01% to about 6% have increased bioavailability (see **FIG. 1**). This is in sharp contrast to Hovgaard-2, which showed relatively low bioavailability (0.5-1%) at the high alkyl glycoside ratios (10:1 and 16:1).

[0150] **FIG. 1** is a graph comparing the bioavailability of the drug MIACALCIN® (salmon calcitonin from Novartis) with and without alkyl glycoside (TDM). MIACALCIN® is a nasal spray and administered directly onto the nasal epithelium or nasal mucosa. **FIG. 1** shows that MIACALCIN® minus alkyl glycoside has very low bioavailability levels in humans (MIACALCIN® product specification insert), as compared to the MIACALCIN® with alkyl gly-

[0150] **FIG. 1** is a graph comparing the bioavailability of the drug MIACALCIN® (salmon calcitonin from Novartis) with and without alkyl glycoside (TDM). MIACALCIN® is a nasal spray and administered directly onto the nasal epithelium or nasal mucosa. **FIG. 1** shows that MIACALCIN® minus alkyl glycoside has very low bioavailability levels in humans (MIACALCIN® product specification insert), as compared to the MIACALCIN® with alkyl gly-

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Preference for TDM


(19) United States
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Padagis US LLC, EX1010

Meezan
EX1010

EXAMPLE 3

Ocular Administration of Alkyl Saccharides Plus Insulin Produces Hypoglycemic Effects In Vivo

[0153] Normal rats were anesthetized with a mixture of xylazine/ketamine to elevate their blood glucose levels. The elevated levels of D-glucose that occur in response to anesthesia provide an optimal system to measure the systemic hypoglycemic action of drug administration, e.g. insulin-containing eye drops. This animal model mimics the hyperglycemic state seen in diabetic animals and humans. In the experimental animal group, anesthetized rats are given eye drops containing insulin. Blood glucose levels from the experimental group are compared to anesthetized animals which rcccivcd cyc drops without insulin. Thc changc in blood glucose levels and the differential systemic responses reflects the effect of insulin absorbed via the route of administration, e.g. ocular route.

[0155] At time 0, after a 50-90 min stabilization period, rats were given 20 μl of eye drops composed of phosphate-buffered saline (PBS) with or without 0.2% regular porcine insulin and 0.125%-0.5% of the absorption enhancing alkyl glycosidc (c.g. TDM) to bc tcstcd. Eyc drops wcrc instillcd

IPR2025-00465, Paper 53 (Sur-Reply) at 19–20

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Preference for TDM

EXAMPLE 4

Ocular and Intranasal Administration of the TDM Plus Insulin Produces Hypoglycemic Effects In Vivo

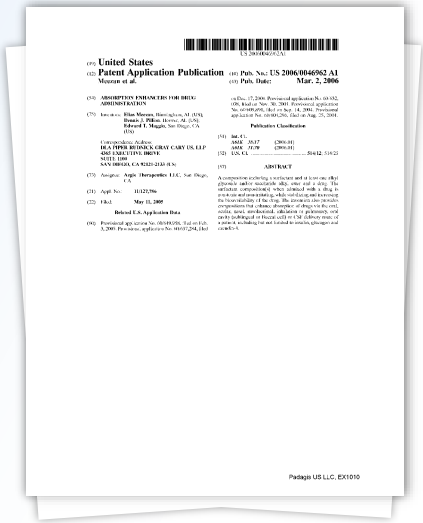
[0163] Since previous Examples showed that administration via eye drops of an absorption enhancer with drug e.g. insulin results in significant absorption of the drug via the nasolacrimal drainage system, therapeutically effective administration of insulin with alkylmaltosides, alkylsucrose and like agents by intranasal administration is tested herein.

[0164] Tetradecylmaltoside (TDM) in combination with insulin also produced a drop in blood D-glucose levels when administered in the form of a drop intranasally as well as via a drop by the ocular route. Eye drops containing 0.2% regular porcine insulin with 0.125% tetradecylmaltoside are administered to rats as previously described. The administration of the composition produces a prompt and prominent drop in blood glucose levels. The drop in blood glucose levels decrease even more by administration of a nose drop containing the same concentration of insulin with 0.5% tetradecylmaltoside (Table II.) Thus, intranasal delivery and administration of the alkyl saccharide with drug results in lowering of blood glucose levels.

Meezan
EX1010

IPR2025-00465, Paper 53 (Sur-Reply) at 19–20

Preference for TDM



Meezan
EX1010

EXAMPLE 5

Ocular Administration of Alkyl Saccharides Plus Insulin Produces Hyperglycemic Effects In Vivo

[0165] Previous studies demonstrated that insulin absorption from the eye is stimulated by saponin, BL-9 and Brij-78. BL-9 and Brij-78 are ineffective at stimulating the absorption of glucagon from the eye, whereas saponin is effective. Glucagon absorption from the eye was measured in rats given eye drops containing various surfactants plus glucagon (30 μg) (Eli Lilly, Indianapolis, Ind.) by monitoring an elevation in blood D-glucose levels. In these experiments, rats were anesthetized with sodium pentobarbital rather than xylazine/ketamin. This modification of the procedure resulted in basal blood glucose levels in the normoglycemic range and made it possible to readily monitor the hyperglycemic action of any glucagon absorbed from the eye.

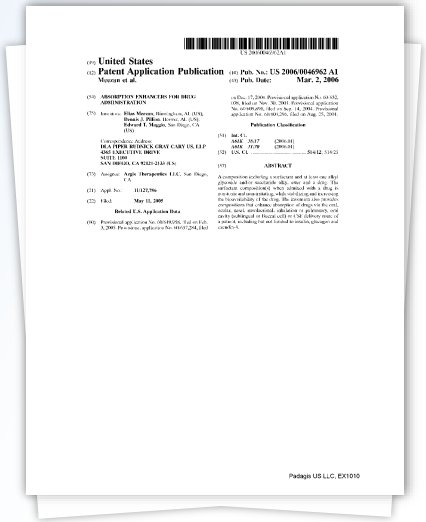
TABLE III

Effect of Eye Drops Containing Insulin or Glucagon and 0.5% Decyl Maltoside, 0.5% Dodecyl Sucrose, or 0.5% Tridecyl Maltoside on Blood Glucose Values in Rats

	Surfactant Agent		
Time (min)	Dodecyl Sucrose	Decyl Maltoside	Tridecyl Maltoside
	Blood Glucose Concentration (mg/dl)		
−20	266	249	255
−10	305	287	307
	Insulin Eye Drops Added		
0	351	337	323
10	347	304	309
20	252	292	217
30	161	221	131
40	120	164	100
50	105	138	87
60	114	114	107
70	113	104	115
80	104	110	79
90	86	120	85
100	113	92	76
110	107	81	74
120	112	87	75
	Glucagon Eye Drops Added		
130	111	95	82
140	143	99	121
150	202	132	148

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Preference for TDM



Meezan
EX1010

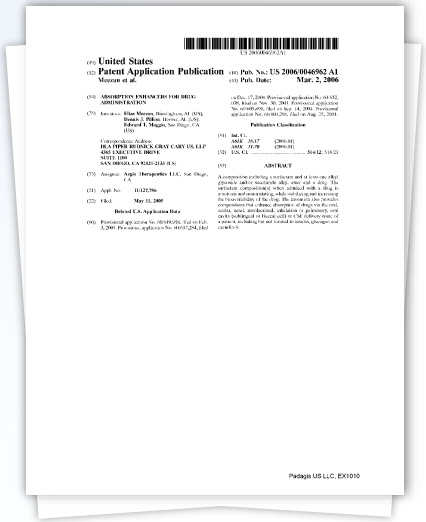
EXAMPLE 6

Intranasal Administration of 0.25% TDM Plus Insulin Decreases Blood Glucose Levels In Vivo

[0167] Intranasal administration of drugs or agents are possible in animal models e.g. mice and rats, although the nasal opening in is very small. In the experiments and results described herein, an anesthesia-induced hyperglycemia model was used (described in Examples above). Hyperglycemic animals were induced by an intraperitoneal (IP) injection containing xylazine-ketamine and blood glucose levels were monitored over a period of time. Immediately after the xylazine-ketamine injection, there was an increase in the blood glucose levels as shown in **FIG. 2** (closed dark circles), and blood glucose levels were about 450 mg/dl. The increase in blood glucose levels was attributed to the inhi-

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Preference for TDM



Meezan
EX1010

EXAMPLE 7

Intranasal Administration of 0.25% TDM (Intravail A)+Exendin-4 Decreases Blood Glucose Levels in Vivo

[0170] The ob/ob mouse model was utilized for the studies described herein. Friedman, J. M., *Nature* 404, 632-634 (2000). All animals received an intraperitoneal (IP) injection of a bolus of 2 g/kg glucose for purposes of determining glucose tolerance. At time 0 the experimental animals were given about 100 micrograms/kg of exendin-4/0.25% TDM (exendin-4 from American Peptide) either as 10 μl of nasal drops (**FIG. 3**; closed triangles), or by IP injection (**FIG. 3**; closed circles), or by and IP injection of saline alone (no drug, no TDM; **FIG. 3**; open circles). Control animals were previously performed and received no drugs. The results of this study are shown in **FIG. 3**.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Preference for TDM

TABLE I

Effect of Eye Drops Containing Insulin Plus Various Concentrations of Dodecyl Maltoside on Blood Glucose Values (in mg/dl) in Rat

	Dodecyl Maltoside Concentration			
	0.125%	0.25%	0.375%	0.50%
Time (min)	Blood Glucose Concentrations (mg/dl)			
−20	305 ± 60	271 ± 38	305 ± 51	375 ± 9
−10	333 ± 58	295 ± 32	308 ± 27	366 ± 12
0	338 ± 67	323 ± 62	309 ± 32	379 ± 4
30	349 ± 64	250 ± 48	212 ± 18	297 ± 18
60	318 ± 38	168 ± 22	134 ± 4	188 ± 25
90	325 ± 57	188 ± 55	125 ± 12	144 ± 13
120	342 ± 78	206 ± 63	119 ± 19	123 ± 5

EX1010 (Meezan) ¶ [0158]

TABLE II

Effect of Insulin Eye Drops, Containing 0.125% Tetradecyl Maltoside and Nose Drops Containing 0.5% Tetradecyl Maltoside on Blood Glucose Values in Rats

Time (min)	Blood Glucose (mg/dl)
−20	319
−10	311
Eye drops added	
0	322
15	335
30	276
45	221
60	212
75	167
90	174
105	167
120	208
Nose Drops Added	
135	129
150	74
165	76
180	68

EX1010 (Meezan) ¶ [0164]

IPR2025-00465, Paper 53 (Sur-Reply) at 19–20

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Preference for TDM

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120	342 ± 78	206 ± 63	119 ± 19	123 ± 5

EX1010 (Meezan) ¶ [0158]

TABLE III

Effect of Eye Drops Containing Insulin or Glucagon and 0.5% Decyl Maltoside, 0.5% Dodecyl Sucrose, or 0.5% Tridecyl Maltoside on Blood Glucose Values in Rats

	Surfactant Agent		
Time (min)	Dodecyl Sucrose	Decyl Maltoside	Tridecyl Maltoside
	Blood Glucose Concentration (mg/dl)		
−20	266	249	255
−10	305	287	307
	Insulin Eye Drops Added		
0	351	337	323
10	347	304	309
20	252	292	217
30	161	221	131
40	120	164	100
50	105	138	87
60	114	114	107
70	113	104	115
80	104	110	79
90	86	120	85
100	113	92	76
110	107	81	74
120	112	87	75
	Glucagon Eye Drops Added		
130	111	95	82
140	143	99	121
150	202	132	148

EX1010 (Meezan) ¶ [0166]

IPR2025-00465, Paper 28 (POR) at 61–62, Paper 53 (Sur-Reply) at 19–20

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE



"[W]here a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness"

In re Kubin, 561 F.3d 1351, 1359 (Fed. Cir. 2009)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Agenda

- No Collateral Estoppel
- Priority Date of '414 and '786 Patents
- Claim Construction
- Non-Obviousness
  - Failure to Disclose All Limitations
  - No Motivation to Combine
- Priority Date of Gwozdz-PCT
- Cartt-'784
- Petitioner's Motion to Strike
- Patent Owner's Motion to Strike
- Patent Owner's Motion to Exclude

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

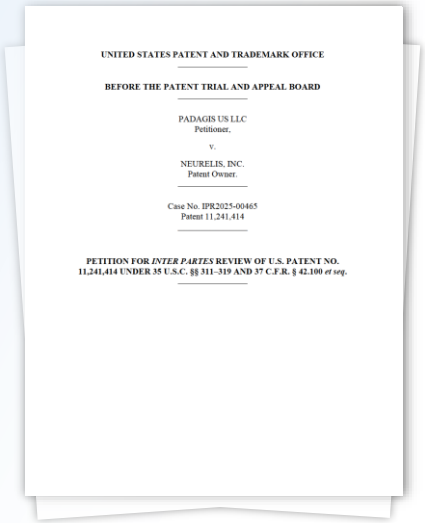
Gwozdz-PCT Is Not Entitled to Its Priority Date

"[T]he cited content" relied on to support the unpatentability analysis must also be "adequately supported by the written description of the provisional application."

In re Riggs, 131 F.4th 1377, 1384-85 (Fed. Cir. 2025)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Petition Relies on "Pharmaceutically Acceptable Additives"


UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PADAGIS US LLC
Petitioner,

v.

NEURELIS, INC.
Patent Owner.

Case No. IPR2025-00465
Patent 11,241,414

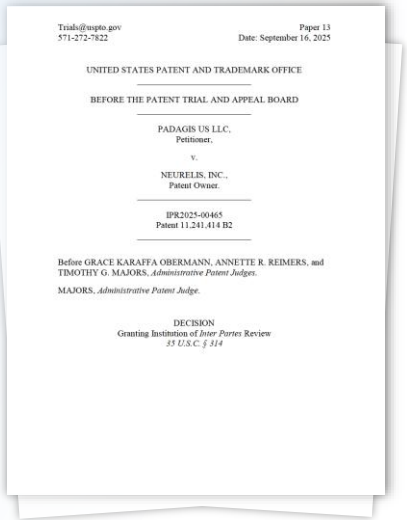
PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 11,241,414 UNDER 35 U.S.C. §§ 311–319 AND 37 C.F.R. § 42.100 *et seq.*

Petition
Paper 2

Moreover, a motivation existed to combine the teachings of Meezan related to alkyl glycosides with the pharmaceutical solutions described in Gwozdz. Gwozdz teaches that the pharmaceutical solutions described therein may further incorporate additional pharmaceutically acceptable additives, including, "acidifying, alkalizing, buffering, chelating, complexing and solubilizing agents, antioxidants and antimicrobial preservatives, penetration enhancers, humectants, suspending and/or viscosity modifying agents, tonicity and wetting or other biocompatible materials" to improve the efficacy. *Id.*, 10:12-16; EX1062, ¶97. Meezan is directed to

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Board Decision



Trials@uspto.gov
571-272-7822

Paper 13
Date: September 16, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PADAGIS US LLC,
Petitioner,

v.

NEURELIS, INC.,
Patent Owner.

IPR2025-00465
Patent 11,241,414 B2

Before GRACE KARAFFA OBERMANN, ANNETTE R. REIMERS, and TIMOTHY G. MAJORS, *Administrative Patent Judges*.

MAJORS, *Administrative Patent Judge*.

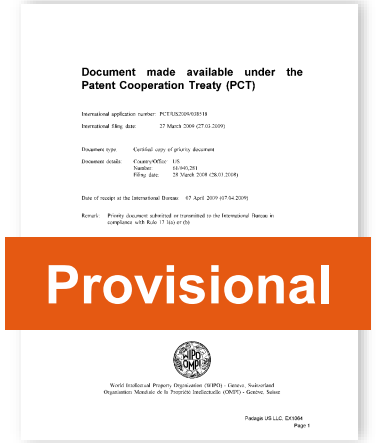
DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

Institution Decision
Paper 13

We agree that at least one portion of Gwozdz is not prior art. To establish that the cited disclosures in Gwozdz are prior art, Petitioner must show support for those disclosures in the Gwozdz Provisional. *In re Riggs*, 131 F.4th 1377, 1384 (Fed. Cir. 2025) (explaining that "the portion of the application relied on . . . as prior art must be supported by the provisional application"). Petitioner did not establish that Gwozdz's disclosure of "penetration enhancers" finds support in the Gwozdz Provisional. Pet. 22. Conversely, Patent Owner shows that the phrase is absent in the Gwozdz Provisional. Prelim. Resp. 34.[18] Based on this record, we determine that Gwozdz's mention of "penetration enhancers" is not prior art to the challenged claims. The phrase cannot, therefore, be used to establish a motivation to combine the asserted references.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

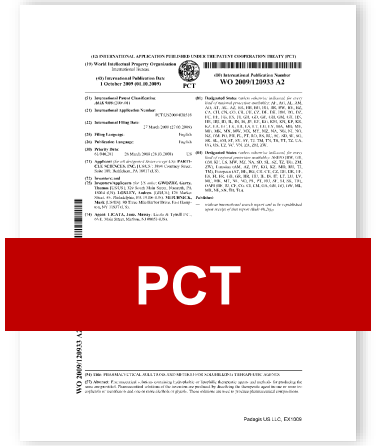
Comparison of Gwozdz PCT and Gwozdz Provisional



Provisional

EX1064

solubilizing agent such as Cremophor. Such pharmaceutical compositions may further contain other pharmaceutically acceptable additives such as, but not limited to, acidifying, alkalizing, buffering, chelating, complexing and solubilizing agents, antioxidants and antimicrobial preservatives, humectants, suspending and/or viscosity modifying agents, tonicity and wetting or other biocompatible materials.



PCT

EX1009

compositions may further contain other pharmaceutically acceptable additives such as, but not limited to, acidifying, alkalizing, buffering, chelating, complexing and solubilizing agents, antioxidants and antimicrobial preservatives, penetration enhancers, humectants, suspending and/or viscosity modifying agents, tonicity and wetting or other biocompatible materials.

IPR2025-00465, EX1064 at 12:10–17; EX1009 at 11:10–17

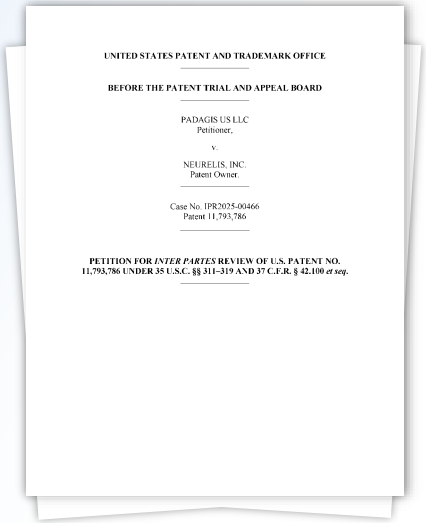
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Agenda

- No Collateral Estoppel
- Priority Date of '414 and '786 Patents
- Claim Construction
- Non-Obviousness
  - Failure to Disclose All Limitations
  - No Motivation to Combine
- Priority Date of Gwozdz-PCT
- Cartt-'784
- Petitioner's Motion to Strike
- Patent Owner's Motion to Strike
- Patent Owner's Motion to Exclude

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Grounds of Invalidity ('786 Patent)


UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PADAGIS US LLC
Petitioner,

v.

NEURELIS, INC.
Patent Owner.

Case No. IPR2025-00466
Patent 11,793,786

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 11,793,786 UNDER 35 U.S.C. §§ 311–319 AND 37 C.F.R. § 42.100 *et seq.*

Petition
Paper 2

IV. IDENTIFICATION OF GROUNDS FOR WHICH REVIEW IS REQUESTED UNDER 37 C.F.R. § 42.104(B)(1)

Petitioner asserts that claims 1-27 of the '786 patent are unpatentable based on the following grounds:

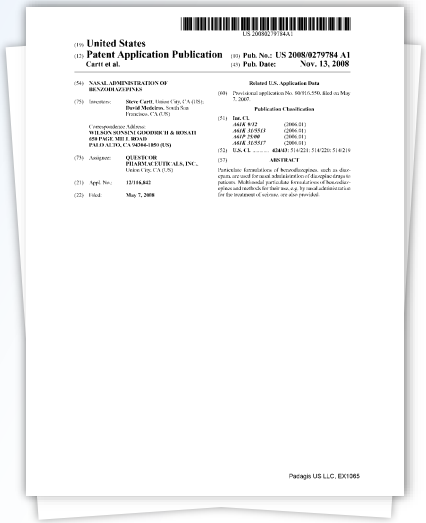
Ground 1: Claims 1-25 are obvious over Gwozdz in view of Meezan.

Ground 2: Claims 20-21 are obvious over Gwozdz in view of Meezan further in view of Cartt.

Ground 3: Claims 26-27 are obvious over Gwozdz in view of Meezan further in view of USP 23/NF 18.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Cartt-784



Cartt-784
EX1065

(19) **United States**
(12) **Patent Application Publication**
Cartt et al.

(10) **Pub. No.: US 2008/0279784 A1**
(43) **Pub. Date: Nov. 13, 2008**

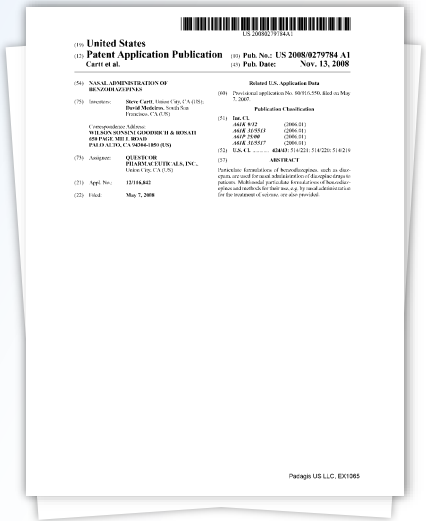
(57) **ABSTRACT**

Particulate formulations of benzodiazepines, such as diazepam, are used for nasal administration of diazepine drugs to patients. Multimodal particulate formulations of benzodiazepines and methods for their use, e.g. by nasal administration for the treatment of seizure, are also provided.

[0015] The foregoing and further needs are further met by embodiments of the present invention, which provide an aerosol composition of an aqueous suspension or dispersion of nanoparticulate benzodiazepine particles, wherein: the droplets of the aerosol have a mass median aerodynamic diameter (MMAD) less than or equal to about 1000 μm and the nanoparticulate benzodiazepine particles have an effective average particle size of less than about 5000 nm.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Cartt-784



Cartt-784
EX1065

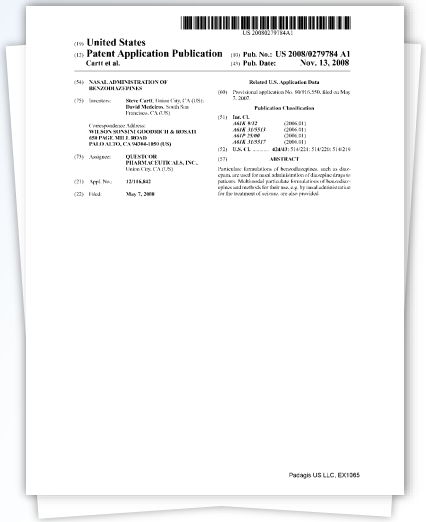
(19) **United States**
(12) **Patent Application Publication**
Cartt et al.

(10) **Pub. No.: US 2008/0279784 A1**
(43) **Pub. Date: Nov. 13, 2008**

[0017] The foregoing and further needs are met by embodiments of the present invention, which provide a method of administering a benzodiazepine drug to a patient, comprising administering to the nose or nasal cavity an effective amount of an aerosol composition of an aqueous suspension or dispersion of nanoparticulate benzodiazepine particles, wherein: the droplets of the aerosol have a mass median aerodynamic diameter (MMAD) less than or equal to about 1000 μm and the nanoparticulate benzodiazepine particles have an effective average particle size of less than about 5000 nm.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Cartt-784



Cartt-784
EX1065

(19) **United States**
(12) **Patent Application Publication**
Cartt et al.
(10) **Pub. No.: US 2008/0279784 A1**
(43) **Pub. Date: Nov. 13, 2008**

[0021] The foregoing and further needs are met by embodiments of the present invention, which provide a non-aqueous dispersion or suspension of nanoparticulate benzodiazepine particles.

[0022] The foregoing and additional needs are further met by embodiments of the present invention, which provide a method of administering a non-aqueous dispersion or suspension of nanoparticulate benzodiazepine particles, the method comprising administering an effective amount of the dispersion or suspension to the nose by administering a therapeutically effective amount of the composition to at least one nostril.

[0023] The foregoing and further needs are additionally met by embodiments of the present invention, which provide, a method of administering a benzodiazepine drug to a patient, comprising administering to the patient's nose or nasal cavity a pharmaceutical composition comprising a non-aqueous dispersion or suspension of nanoparticulate benzodiazepine particles.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Dr. Donovan Testimony

Dr. Donovan

Q. Certainly. Not as a criticism, but just to make the record clear, in the eleven minutes that you took to review Cartt, did you identify any embodiments in Cartt of a formulation that did not include particulates?

A. And so I didn't look through every paragraph to see if there was an embodiment hidden in there. Looking at the examples, all of the examples contained particles containing an active pharmaceutical ingredient.

Q. Okay. Thank you.

EX2070 at 177:14–25

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Agenda

- No Collateral Estoppel
- Priority Date of '414 and '786 Patents
- Claim Construction
- Non-Obviousness
  - Failure to Disclose All Limitations
  - No Motivation to Combine
- Priority Date of Gwozdz-PCT
- Cartt-'784
- Petitioner's Motion to Strike
- Patent Owner's Motion to Strike
- Patent Owner's Motion to Exclude

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Inventor Declarations of Limited Scope

issues related to the depositions of the inventor-declarants. EX3004. On January 5, 2026, Patent Owner filed its Response to the Petition, in which it relied on the Inventor Declarations to support its argument that the Gwozdz[2] prior art reference does not qualify as prior art. *See, e.g.*, Paper 28 at 36. Specifically, Patent Owner



"For cross-examination testimony, the scope of the examination is limited to the scope of the direct testimony."

37 C.F.R. § 42.53(d)(5)(ii)

IPR2025-00465, Paper 44 (Mot. to Strike) at 2.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Provisions of 35 U.S.C. § 103(C) (pre-AIA)

(1) Subject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the claimed invention was made, owned by the same person or subject to an obligation of assignment to the same person.

(2) For purposes of this subsection, subject matter developed by another person and a claimed invention shall be deemed to have been owned by the same person or subject to an obligation of assignment to the same person if —



(A) the claimed invention was made by or on behalf of parties to a joint research agreement that was in effect on or before the date the claimed invention was made;

(B) the claimed invention was made as a result of activities undertaken within the scope of the joint research agreement; **and**

(C) the application for patent for the claimed invention discloses or is amended to disclose the names of the parties to the joint research agreement.

(3) For purposes of paragraph (2), the term "joint research agreement" means a written contract, grant, or cooperative agreement entered into by two or more persons or entities for the performance of experimental, developmental, or research work in the field of the claimed invention.

35 U.S.C. § 103(C) (pre-AIA)

IPR2025-00465, Paper 28 (POR) at 32–33.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE



(2) For purposes of this subsection, subject matter developed by another person and a claimed invention shall be deemed to have been owned by the same person or subject to an obligation of assignment to the same person if—

(A) the claimed invention was made by or on behalf of parties to a joint research agreement that was in effect on or before the date the claimed invention was made;

(B) the claimed invention was made as a result of activities undertaken within the scope of the joint research agreement; and

(C) the application for patent for the claimed invention discloses or is amended to disclose the names of the parties to the joint research agreement.

35 U.S.C. § 103(C)(2) (pre-AIA)

The safe harbor of §103(c)(2) requires disclosure of the parties to the joint research agreement ("JRA"). POR, 32-39. Per the Board's March 20, 2026 Decision (Paper 39, 15), the Board denied Patent Owner's rehearing request seeking leave to petition for a certificate of correction ("CoC") to add the JRA to the '414 Patent. The '414 Patent as issued therefore does not disclose the JRA parties, so Patent Owner's argument is moot.

IPR2025-00465, Paper 43 (Pet. Reply) at 25.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

No Need to Expunge Exhibits

"Although Petitioner further requests that we expunge [the declaration], we decline to do so in interest of a complete record upon any appeal."

New World Med., Inc. v. Microsurgical Tech., Inc., IPR2020-01573, Paper 49 at 5 & n.3 (P.T.A.B. Nov. 5, 2021)

"Rather than striking any material from the record, we adopt a practical approach that preserves the record for appeal."

3M Co. v. Bay Materials, LLC, IPR2022-01214, Paper 77 at 40 (P.T.A.B. Jan. 16, 2024)

IPR2025-00465, Paper 46 (Opp. to Mot. to Strike) at 7–8

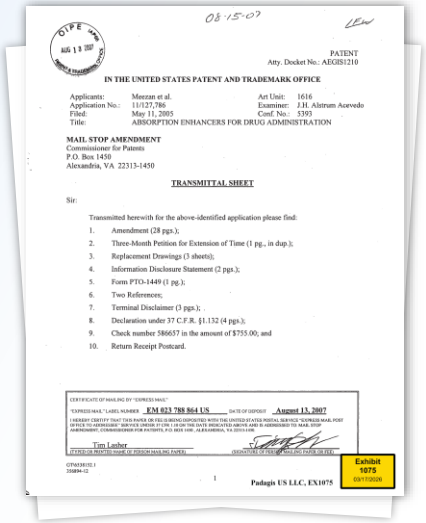
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Agenda

- No Collateral Estoppel
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  - Failure to Disclose All Limitations
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- Priority Date of Gwozdz-PCT
- Cartt-'784
- Petitioner's Motion to Strike
- Patent Owner's Motion to Strike
- Patent Owner's Motion to Exclude

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

New Exhibits in Reply



PATENT
Atty. Docket No.: ADGBS1210

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Meezan et al. Art Unit: 1616
Application No.: 11/127,786 Examiner: J.H. Alstrum Acevedo
Filed: May 11, 2005 Conf. No.: 5393
Title: ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL SHEET

Sir:

Transmitted herewith for the above-identified application please find:

1. Amendment (28 pgs.);
2. Three-Month Petition for Extension of Time (1 pg., in dup.);
3. Replacement Drawings (3 sheets);
4. Information Disclosure Statement (2 pgs.);
5. Form PTO-1449 (1 pg.);
6. Two References;
7. Terminal Disclaimer (3 pgs.);
8. Declaration under 37 C.F.R. §1.132 (4 pgs.);
9. Check number 586657 in the amount of $755.00; and
10. Return Receipt Postcard.

"EXPRESS MAIL" LABEL NUMBER EM 023 788 864 US DATE OF DEPOSIT August 13, 2007

Tim Lauber

Exhibit 1075

Padagis US LLC, EX1075

EX1075

Please replace paragraph [0117] of the specification with the following amended paragraph:

[0117] Stability of the alkyl glycoside depends, in part, on the number of carbon atoms, or ~~branching~~ length of the alkyl chain, with tetradecylmaltoside (TDM) having the greatest effect; but other ~~highly branched~~ long alkyl chains including DDM also have stabilizing effects. In contrast to Hovgaard-1, which described the preference for a high alkyl glycoside to drug ratio, the instant invention shows that this ratio is much lower. For example, alkyl glycosides in the range of about 0.01% to about 6% by weight result in good stabilization of the drug; whereas Hovgaard-1 shows stabilization is only achieved at much higher ratios of alkyl glycosides to drug (10:1 and 16:1). Even more interesting, alkyl glycosides of the invention in the range of about 0.01% to about 6% have increased bioavailability (see FIG. 1). This is in sharp contrast to Hovgaard-2, which showed relatively low bioavailability (0.5-1%) at the high alkyl glycoside ratios (10:1 and 16:1).

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

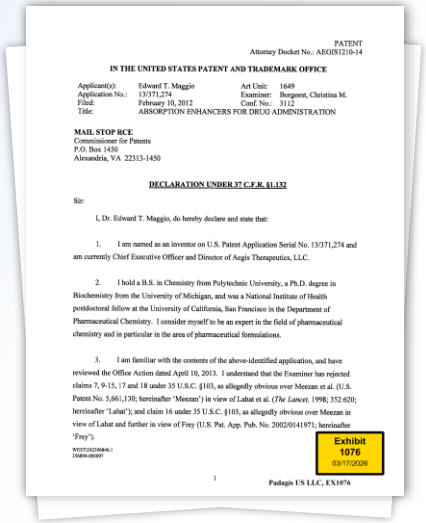
Apple Inc., v. DoDots Licensing Solutions

"[T]here is no sufficient indication on this record to establish a reasonable likelihood that the [challenged exhibits] are available prior art for an inter partes review, as they are not part of the patent."

Apple Inc., v. DoDots Licensing Solutions LLC, IPR2023-00939, Paper 12 at 15-17 (P.T.A.B. Jan. 3, 2024)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

New Exhibits in Reply



PATENT
Attorney Docket No.: AEGIS1210-14

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Edward T. Maggio	Art Unit:	1649
Application No.:	13/371,274	Examiner:	Borgeest, Christina M.
Filed:	February 10, 2012	Conf. No.:	3112
Title:	ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION		

MAIL STOP RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132

Sir:

I, Dr. Edward T. Maggio, do hereby declare and state that:

1. I am named as an inventor on U.S. Patent Application Serial No. 13/371,274 and am currently Chief Executive Officer and Director of Aegis Therapeutics, LLC.

2. I hold a B.S. in Chemistry from Polytechnic University, a Ph.D. degree in Biochemistry from the University of Michigan, and was a National Institute of Health postdoctoral fellow at the University of California, San Francisco in the Department of Pharmaceutical Chemistry. I consider myself to be an expert in the field of pharmaceutical chemistry and in particular in the area of pharmaceutical formulations.

3. I am familiar with the contents of the above-identified application, and have reviewed the Office Action dated April 10, 2013. I understand that the Examiner has rejected claims 7, 9-15, 17 and 18 under 35 U.S.C. §103, as allegedly obvious over Meezan et al. (U.S. Patent No. 5,661,130; hereinafter 'Meezan') in view of Lahat et al. (*The Lancet*, 1998; 352:620; hereinafter 'Lahat'); and claim 16 under 35 U.S.C. §103, as allegedly obvious over Meezan in view of Lahat and further in view of Frey (U.S. Pat. App. Pub. No. 2002/0141971; hereinafter 'Frey').

Exhibit 1076 03/17/2026

1

Padagis US LLC, EX1076

EX1076

5. The present invention is based on the discovery that the alkyl glycoside, dodecyl-β-D-maltoside (also referred to as n-dodecyl-β-D-maltoside), increases absorption of therapeutic agents to the cerebral spinal fluid (CSF) of the central nervous system (CNS) of a subject upon nasal administration.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Dr. Donovan Did Not Know the Meaning of "n-"

Dr. Donovan

Q. Do you have an understanding of what that "n" prefix means in the context of n-Dodecyl-beta-D-maltoside?

A. It's a structural arrangement indicator that escapes me at the moment.

Q. If I told you it it's an indicator that stands for "normal," would that make sense?

A. Oh, I -- it -- I mean, it makes sense because it's in keeping that I know that what "n" -- I know that's what "n" stands for, but what "normal" is being attributed to is where I -- I'm not willing to state that I know that clearly right now.

Q. You don't recall what structural information the "n" conveys in n-Dodecyl-beta-D-maltoside; is that correct?

A. Not at this moment to testify to.

Q. Okay. And that's not an issue you investigated in the course of forming your opinions in this case, correct?

A. Not for a very long time. I probably looked at a description of n-Dodecyl-beta-D-maltoside and noted it, but it didn't stick.

EX2070 at 193:2–25

EX2070 at 193:2–25

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Agenda

- No Collateral Estoppel
- Priority Date of '414 and '786 Patents
- Claim Construction
- Non-Obviousness
  - Failure to Disclose All Limitations
  - No Motivation to Combine
- Priority Date of Gwozdz-PCT
- Cartt-'784
- Petitioner's Motion to Strike
- Patent Owner's Motion to Strike
- Patent Owner's Motion to Exclude

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Uncited Exhibits Should Be Excluded for Relevance



"The Board may exclude or give no weight to the evidence where a party has failed to state its relevance or to identify specific portions of the evidence that support the challenge."

37 C.F.R. § 42.104(b)(5)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Uncited Exhibits Should Be Excluded for Relevance

Exhibit	Cited by Petitioner	Cited by Dr. Donovan
EX1073	✗	✓
EX1074	✗	✗
EX1075	✗	✓
EX1076	✓	✓
EX1080	✗	✗

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

EX1075 and EX1076 Should Be Excluded for Hearsay



"(c) Hearsay. "Hearsay" means a statement that:

(1) the declarant does not make while testifying at the current trial or hearing; and

(2) a party offers in evidence to prove the truth of the matter asserted in the statement."

Federal Rule of Evidence 801

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Dr. Donovan's Reliance on EX1075



UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PADAGIS US LLC,

Petitioner,

v.

NEURELIS, INC.,

Patent Owner.

Case No. IPR2025-00465
U.S. Patent No. 11,241,414

REPLY DECLARATION OF MAUREEN DONOVAN, PH.D. IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 11,241,414

PAGE 1

Padagis US LLC, EX1078

EX1078

on this issue are incorrect. Rather, the ***correct*** Meezan specification emphasizes and supports my opinions: a POSA would understand that Meezan discloses alkyl glycosides having straight-chain (i.e., "long") alkyl groups, ***not*** branched structures. Indeed, the corrected language above *specifically* emphasizes that "DDM" has a "long alkyl chain[]." *Id.*

EX1078 at 25–26

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Rule 703



"An expert may base an opinion on facts or data in the case that the expert has been made aware of or personally observed. If experts in the particular field would reasonably rely on those kinds of facts or data in forming an opinion on the subject, they need not be admissible for the opinion to be admitted."

Federal Rules of Evidence 703

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Challenged Patents

Table of Independent Claim of U.S. Patent No. 11,241,414

Claim Element	Claim Language from '414 Patent
1(Preamble)	1. A pharmaceutical solution for nasal administration consisting of:
1(a)	diazepam or a pharmaceutically acceptable salt thereof;
1(b)	one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from 30% to 95% (w/w);
1(c)	ethanol and benzyl alcohol in a combined amount from 10% to 70% (w/w); and
1(d)	n-dodecyl beta-D-maltoside.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Table of Dependent Claims of U.S. Patent No. 11,241,414

Claim Language from '414 Patent
2. The pharmaceutical solution of claim 1, wherein the diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 1 to 20% (w/v).
3. The pharmaceutical solution of claim 1, wherein the diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 10 mg/mL to 250 mg/mL.
4. The pharmaceutical solution of claim 3, wherein the diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 20 mg/mL to 50 mg/mL.
5. The pharmaceutical solution of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, and any combinations thereof.
6. The pharmaceutical solution of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from 45% to 85% (w/w).
7. The pharmaceutical solution of claim 6, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from 60% to 75% (w/w).
8. The pharmaceutical solution of claim 1, wherein the ethanol and benzyl alcohol is in a combined amount from 15% to 55% (w/w).
9. The pharmaceutical solution of claim 8, wherein the ethanol and benzyl alcohol is in a combined amount from 25% to 40% (w/w).

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Table of Dependent Claims of U.S. Patent No. 11,241,414

Claim Language from '414 Patent
10. The pharmaceutical solution of claim 1, wherein the solution consists of diazepam, vitamin E, ethanol, benzyl alcohol, and n-dodecyl beta-D-maltoside.
11. A pharmaceutical solution for nasal administration consisting of: diazepam or a pharmaceutically acceptable salt thereof; one or more natural or synthetic α-tocopherols, or any combinations thereof, in an amount from 30% to 95% (w/w); ethanol and benzyl alcohol in a combined amount from 10% to 70% (w/w); and n-dodecyl beta-D-maltoside.
12. The pharmaceutical solution of claim 11, wherein the diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 1 to 20% (w/v).
13. The pharmaceutical solution of claim 11, wherein the diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 10 mg/mL to 250 mg/mL.
14. The pharmaceutical solution of claim 13, wherein the diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 20 mg/mL to 50 mg/mL.
15. The pharmaceutical solution of claim 11, wherein the one or more natural or synthetic α-tocopherols, or any combinations thereof is in an amount from 45% to 85% (w/w).
16. The pharmaceutical solution of claim 15, wherein the one or more natural or synthetic α-tocopherols, or any combinations thereof is in an amount from 60% to 75% (w/w).
17. The pharmaceutical solution of claim 11, wherein the ethanol and benzyl alcohol is in a combined amount from 15% to 55% (w/w).
18. The pharmaceutical solution of claim 17, wherein the ethanol and benzyl alcohol is in a combined amount from 25% to 40% (w/w).

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Table of Independent Claims of U.S. Patent No. 11,793,786

Claim Element	Claim Language from '786 Patent
1(Preamble)	1. A pharmaceutical solution for nasal administration consisting of:
1(a)	a therapeutically effective amount of diazepam or a pharmaceutically acceptable salt thereof;
1(b)	one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any isomers thereof, any esters thereof, and any combinations thereof, in an amount from 30% to 95% (w/w);
1(c)	one or more alcohols in an amount from 10% to 70% (w/w), wherein the one or more alcohols comprises benzyl alcohol; and
1(d)	n-dodecyl beta-D-maltoside.
11(Preamble)	11. A pharmaceutical solution for nasal administration consisting of:
11(a)	a therapeutically effective amount of diazepam or a pharmaceutically acceptable salt thereof;
11(b)	one or more natural or synthetic α-tocopherols selected from the group consisting of tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, tocophersolan, any isomers thereof, any esters thereof, and any combinations thereof, in an amount from 30% to 95% (w/w);
11(c)	one of more alcohols in an amount from 10% to 70% (w/w)), wherein the one or more alcohols comprises benzyl alcohol;
11(d)	and n-dodecyl beta-D-maltoside.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Table of Dependent Claims of U.S. Patent No. 11,793,786

Claim Language from '786 Patent
2. The pharmaceutical solution of claim 1, wherein the therapeutically effective amount of diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 1 to 20% (w/v).
3. The pharmaceutical solution of claim 1, wherein the therapeutically effective amount of diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 10 mg/mL to 250 mg/mL.
4. The pharmaceutical solution of claim 3, wherein the therapeutically effective amount of diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 20 mg/mL to 50 mg/mL.
5. The pharmaceutical solution of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols is in an amount from 45% to 85% (w/w).
6. The pharmaceutical solution of claim 5, wherein the one or more natural or synthetic tocopherols or tocotrienols is in an amount from 60% to 75% (w/w).
7. The pharmaceutical solution of claim 1, wherein the one or more alcohols is benzyl alcohol and a second alcohol selected from ethanol, propyl alcohol, butyl alcohol, pentanol, any isomers thereof, and any combinations thereof.
8. The pharmaceutical solution of claim 1, wherein the one or more alcohols are in an amount from 15% to 55% (w/w).
9. The pharmaceutical solution of claim 8, wherein the one or more alcohols are in an amount from 25% to 40% (w/w).

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Table of Dependent Claims of U.S. Patent No. 11,793,786

Claim Language from '786 Patent
10. The pharmaceutical solution of claim 1, wherein the solution consists of diazepam, vitamin E, benzyl alcohol, and n-dodecyl beta-D-maltoside.
12. The pharmaceutical solution of claim 11, wherein the therapeutically effective amount of diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 1 to 20% (w/v).
13. The pharmaceutical solution of claim 11, wherein the therapeutically effective amount of diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 10 mg/mL to 250 mg/mL.
14. The pharmaceutical solution of claim 13, wherein the therapeutically effective amount of diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 20 mg/mL to 50 mg/mL.
15. The pharmaceutical solution of claim 11, wherein the one or more natural or synthetic tocopherols is in an amount from 45% to 85% (w/w).
16. The pharmaceutical solution of claim 15, wherein the one or more natural or synthetic tocopherols is in an amount from 60% to 75% (w/w).
17. The pharmaceutical solution of claim 11, wherein the one or more alcohols is benzyl alcohol and a second alcohol selected from ethanol, propyl alcohol, butyl alcohol, pentanol, any isomers thereof, and any combinations thereof.
18. The pharmaceutical solution of claim 11, wherein the one or more alcohols are in an amount from 15% to 55% (w/w).

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

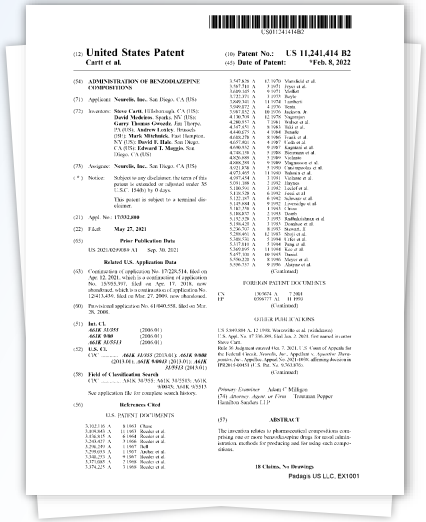
Table of Claims of U.S. Patent No. 8,895,546

Claim Element	Claim Language from '546 Patent
1(Preamble)*	1. A pharmaceutical Solution for nasal administration consisting of:
1(a)*	a benzodiazepine drug;
1(b)*	one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w):
1(c)*	ethanol and benzyl alcohol in a combined amount from about 10% to about 70% (w/w); and
1(d)*	an alkyl glycoside.
15*	15. The pharmaceutical solution of claim 1, wherein the alkyl glycoside is present in pharmaceutical solution in a concentration of at least about 0.01% (w/w).
16*	16. The pharmaceutical solution of claim 15, wherein the alkyl glycoside is present in the pharmaceutical solution in an amount of 0.01% to 1% (w/w).
17	17. The solution of claim 1, consisting of diazepam, Vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.
22	22. The solution of claim 16, wherein the alkyl glycoside is dodecyl maltoside.

* Claims 1, 15, and 16 have been statutorily disclaimed.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

'414 Patent Claim 1



'414 Patent

What is claimed is:

1. A pharmaceutical solution for nasal administration consisting of:

diazepam or a pharmaceutically acceptable salt thereof;

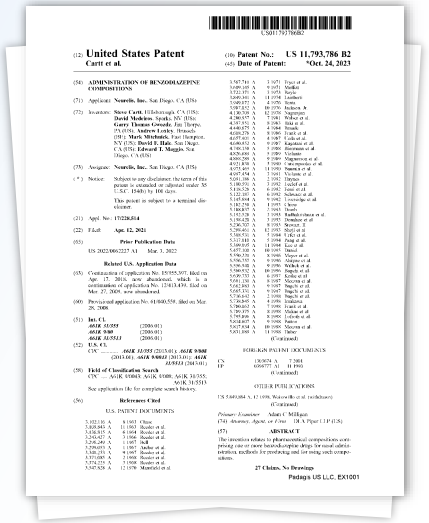
one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from 30% to 95% (w/w);

ethanol and benzyl alcohol in a combined amount from 10% to 70% (w/w); and

n-dodecyl beta-D-maltoside.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

'786 Patent Claim 1



'786 Patent

What is claimed is:

1. A pharmaceutical solution for nasal administration consisting of:

a therapeutically effective amount of diazepam or a pharmaceutically acceptable salt thereof;

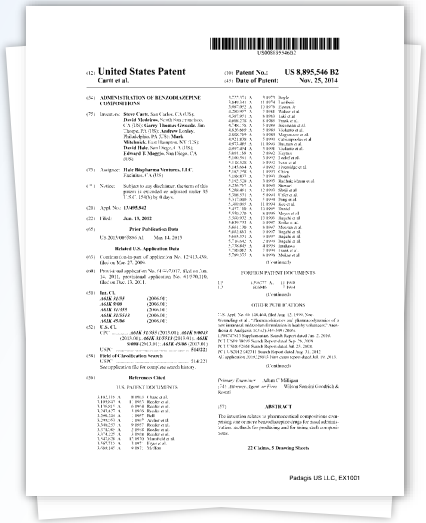
one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any isomers thereof, any esters thereof, and any combinations thereof, in an amount from 30% to 95% (w/w);

one or more alcohols in an amount from 10% to 70% (w/w), wherein the one or more alcohols comprises benzyl alcohol; and

n-dodecyl beta-D-maltoside.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

'546 Patent Claims 17 and 22



'546 Patent

What is claimed is:

1. A pharmaceutical solution for nasal administration consisting of:

(a) a benzodiazepine drug;

(b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w);

(c) ethanol and benzyl alcohol in a combined amount from about 10% to about 70% (w/w); and

(d) an alkyl glycoside.

15. The pharmaceutical solution of claim 1, wherein the alkyl glycoside is present in pharmaceutical solution in a concentration of at least about 0.01% (w/w).

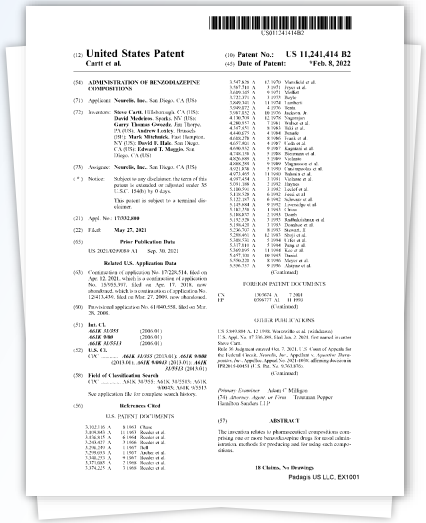
16. The pharmaceutical solution of claim 15, wherein the alkyl glycoside is present in the pharmaceutical solution in an amount of 0.01% to 1% (w/w).

17. The solution of claim 1, consisting of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.

22. The solution of claim 16, wherein the alkyl glycoside is dodecyl maltoside.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

'414 Patent Claim 1



'414 Patent

What is claimed is:

1. A pharmaceutical solution for nasal administration consisting of:

diazepam or a pharmaceutically acceptable salt thereof;

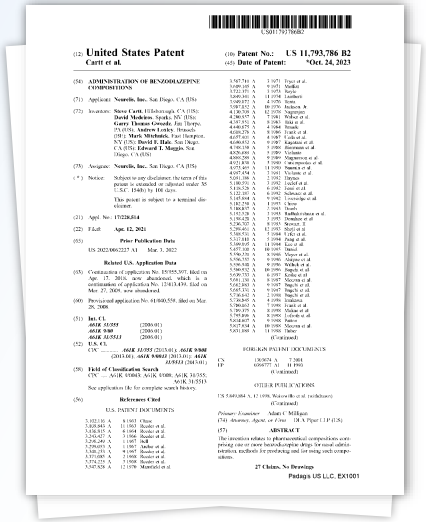
one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from 30% to 95% (w/w);

ethanol and benzyl alcohol in a combined amount from 10% to 70% (w/w); and

n-dodecyl beta-D-maltoside.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

'786 Patent Claim 1



'786 Patent

What is claimed is:

1. A pharmaceutical solution for nasal administration consisting of:

a therapeutically effective amount of diazepam or a pharmaceutically acceptable salt thereof;

one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any isomers thereof, any esters thereof, and any combinations thereof, in an amount from 30% to 95% (w/w);

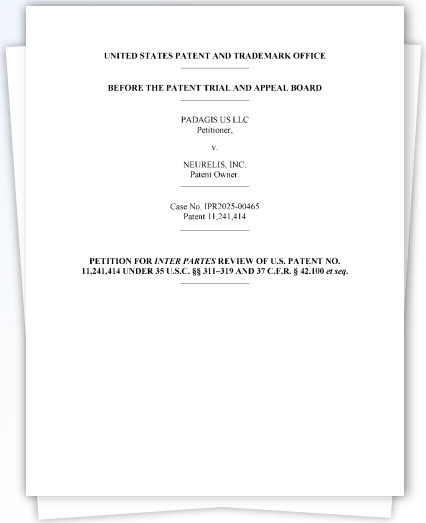
one or more alcohols in an amount from 10% to 70% (w/w), wherein the one or more alcohols comprises benzyl alcohol; and

n-dodecyl beta-D-maltoside.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Grounds of Invalidity

Grounds of Invalidity ('414 Patent)



UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PADAGIS US LLC
Petitioner,

v.

NEURELIS, INC.
Patent Owner.

Case No. IPR2025-00465
Patent 11,241,414

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 11,241,414 UNDER 35 U.S.C. §§ 311–319 AND 37 C.F.R. § 42.100 *et seq.*

Paper 2
Petition

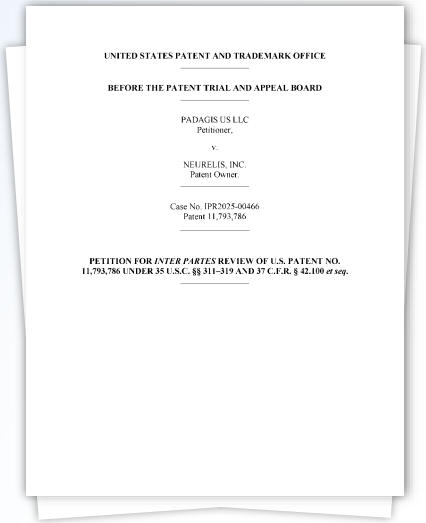
IV. IDENTIFICATION OF GROUNDS FOR WHICH REVIEW IS REQUESTED UNDER 37 C.F.R. § 42.104(B)(1)

Petitioner asserts that claims 1-18 of the '414 patent are unpatentable based on the following ground:

Ground 1: Claims 1-18 are obvious over Gwozdz[1] in view of Meezan[2].

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Grounds of Invalidity ('786 Patent)



UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PADAGIS US LLC
Petitioner,

v.

NEURELIS, INC.
Patent Owner.

Case No. IPR2025-00466
Patent 11,793,786

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 11,793,786 UNDER 35 U.S.C. §§ 311–319 AND 37 C.F.R. § 42.100 *et seq.*

Paper 2
Petition

IV. IDENTIFICATION OF GROUNDS FOR WHICH REVIEW IS REQUESTED UNDER 37 C.F.R. § 42.104(B)(1)

Petitioner asserts that claims 1-27 of the '786 patent are unpatentable based on the following grounds:

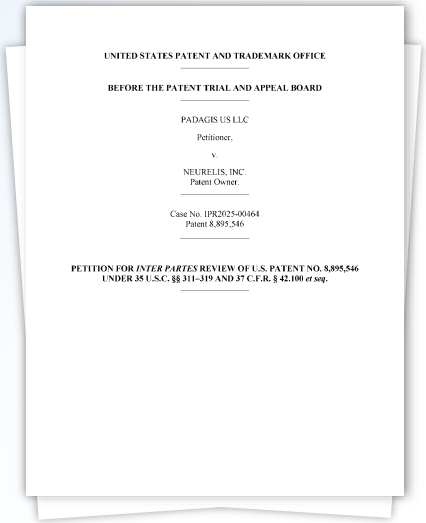
Ground 1: Claims 1-25 are obvious over Gwozdz in view of Meezan.

Ground 2: Claims 20-21 are obvious over Gwozdz in view of Meezan further in view of Cartt.

Ground 3: Claims 26-27 are obvious over Gwozdz in view of Meezan further in view of USP 23/NF 18.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ground of Invalidity ('546 Patent)



UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PADAGIS US LLC
Petitioner,
v.
NEURELIS, INC
Patent Owner.

Case No. IPR2025-00464
Patent 8,895,546

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,895,546
UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. § 42.100 *et seq.*

Paper 2
Petition

IV. IDENTIFICATION OF GROUNDS FOR WHICH REVIEW IS REQUESTED UNDER 37 C.F.R. § 42.104(B)(1)

Petitioner asserts that claims 1-22 of the '546 patent are unpatentable based on the following grounds:

Ground 1: Claims 1-22 are obvious over Gwozdz[1] in view of Meezan[2].

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE