Patent Owner's Demonstratives

United Therapeutics Corporation v. Liquidia Technologies, Inc.

IPR2021-00406 – U.S. Patent No. 10,716,793

May 13, 2022

Challenged Claims are Novel and Non-obvious

1. A method of treating pulmonary hypertension comprising administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof with an inhalation device, wherein the therapeutically effective single event dose comprises from 15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 3 breaths.
2. The method of claim 1, wherein the inhalation device is a soft mist inhaler.
3. The method of claim 1, wherein the inhalation device is a pulsed ultrasonic nebulizer.
4. The method of claim 1, wherein the inhalation device is a dry powder inhaler.
5. The method of claim 1, wherein the inhalation device is a pressurized metered dose inhaler.
6. The method of claim 4, wherein the formulation is a powder.
7. The method of claim 6, wherein the powder comprises particles less than 5 micrometers in diameter.
8. The method of claim 1, wherein the formulation contains no metacresol.

No **prior art** disclosure of the **claimed therapeutically effective dose** delivered in **1-3 breaths**

Source: Paper No. 2 (Petition), 3-4.

Grounds 1-6

Ground	Basis	'793 Claims	'212 Patent (EX1006)	JESC (EX1007)	JAHA (EX1008)	Ghofrani (EX1010)	Vos. 2006 (EX1009)
1	§103	1-8	X	X	X		
2	§103	1-8	X	X			
3	§102	1				X	
4	§103	1, 3, 8			X	X	
5	§102	1, 3					X
6	§103	2, 4-8	X				X

Source: Paper No. 2, 3-4.

Petition: One Narrow Basis for Institution

Institution Decision

- **Grounds 1 ('212 + JAHA + JESC) and 2 ('212 + JESC)**
  - Petition's 1st calculation found to show a dose within 15-90 µg (ID 27-29)
  - Petition's 2nd calculation did not yield a dose within 15-90 µg (ID 29-30)
- **Grounds 3-6**
  - Board agreed Ghofrani and Voswinckel 2006 were not "by others"
  - Only instituted pursuant to *SAS Institute Inc. v. Iancu*, 138 S. Ct. 1348, 1355–56 (2018)

Liquidia's initial calculation:

- Based on faulty hindsight assumptions
- Alleged "confirm[ation]" reference does not corroborate POSA general knowledge

Liquidia's shifting sands calculations are belated and still have major flaws

Liquidia waived depositions and failed to develop further evidence

Source: Paper No. 18 (Institution Decision or "ID"), 27-30, 37-43.

Grounds 3-6: Ghofrani and Voswinckel Not "By Others"

Ground	Basis	'793 Claims	'212 Patent (EX1006)	JESC (EX1007)	JAHA (EX1008)	Ghofrani (EX1010)	Vos 2006 (EX1009)
1	§103	1-8	X	X	X		
2	§103	1-8	X	X			
~~3~~	~~§102~~	~~1~~				~~X~~	
~~4~~	~~§103~~	~~1, 3, 8~~			~~X~~	~~X~~	
~~5~~	~~§102~~	~~1, 3~~					~~X~~
~~6~~	~~§103~~	~~2, 4-8~~	~~X~~				~~X~~

Source: Paper No. 2, 3-4.

Grounds 1-2: JESC And JAHA Not "Publicly Available"

Ground	Basis	'793 Claims	'212 Patent (EX1006)	JESC (EX1007)	JAHA (EX1008)	Ghofrani (EX1010)	Vos. 2006 (EX1009)
~~1~~	~~§103~~	~~1-8~~	~~X~~	~~X~~	~~X~~		
~~2~~	~~§103~~	~~1-8~~	~~X~~	~~X~~			
3							
4							
5							X
6	§103	2, 4-8	X				X

JESC and JAHA are not prior art

- Absence of evidence in Petition
- Untimely new evidence

Sources: Paper No. 2, 3-4; Paper No. 29 (Patent Owner Response), 12-18; Paper No. 55 (Patent Owner Sur-Reply), 2-3.

Grounds 1-2: Substantive Flaws

Ground	Basis	'793 Claims	'212 Patent (EX1006)	JESC (EX1007)	JAHA (EX1008)	Ghofrani (EX1010)	Vos. 2006 (EX1009)
~~1~~	~~§103~~	1-8	X	X	X		
~~2~~	~~§103~~	1-8	X	X			
3							
4							
5							X
6	§103	2, 4-8	X				X

- No dose
- Dr. Hill: no teaching of "therapeutically effective"
- No reasonable expectation of success

Sources: Paper No. 2, 3-4; Paper No. 29, 18-24; Paper No. 55, 11-19.

Ghofrani & Voswinckel 2006 Are Not Prior Art "By Others"

Ghofrani and Voswinckel 2006 are Not Prior Art “By Others”

Herz © Urban & Vogel 2005

Neue Therapieoptionen in der Behandlung der pulmonalarteriellen Hypertonie

Hossein Ardeschir Ghofrani, Robert Voswinckel, Frank Reichenberger, Friedrich Grimminger, Werner Seeger[1]

Zusammenfassung

grund der längeren Wirkung einen Vorteil gegenüber dem bereits zugelassenen inhalierten Iloprost haben. Bisher stehen jedoch noch Ergebnisse einer kontrollierten randomisierten Studie aus, die die Wirksamkeit dieser Therapie in der chronischen Anwendung dokumentieren. Der selektive Phosphodiesterase-5-(PDE5-)Inhibitor Sildenafil ist im Vergleich zu den

Emerging Therapies

Abstract

296

17 January 2006 | Annals of Internal Medicine | Volume 144 Number 2

Annals of Internal Medicine

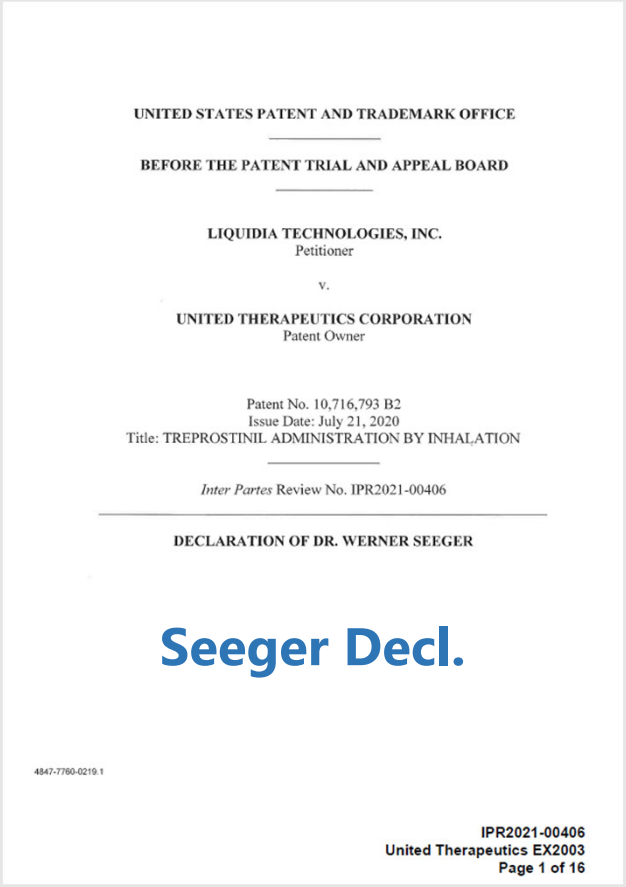
www.annals.org | Established in 1927 by the American College of Physicians

Liquidia's Exhibit 1009
Page 1

- Less than 1 year before priority date
- No evidence of “by others”
- Inventors’ own work
- Liquidia’s failed burden

Sources: Paper No. 29, 44-54; Paper No. 55, 25; EX1009; EX2003; EX2004; EX2005; EX2006.

Seeger Declaration Explains Ghofrani Authorship



UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LIQUIDIA TECHNOLOGIES, INC.
Petitioner

v.

UNITED THERAPEUTICS CORPORATION
Patent Owner

Patent No. 10,716,793 B2
Issue Date: July 21, 2020
Title: TREPROSTINIL ADMINISTRATION BY INHALATION

Inter Partes Review No. IPR2021-00406

DECLARATION OF DR. WERNER SEEGER

Seeger Decl.

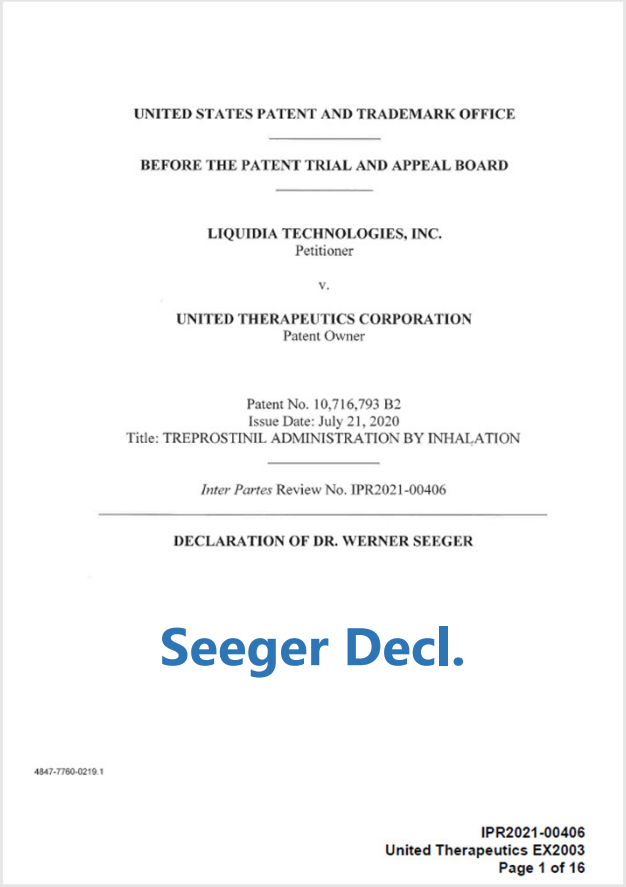
4847-7760-0219.1

IPR2021-00406
United Therapeutics EX2003
Page 1 of 16

- Dr. Seeger's declaration is **unrebutted**
- Ghofrani:
  - "Initial trials in Giessen" section is the inventors' work
  - Non-inventors did not contribute to the section Liquidia relies upon as alleged prior art
  - Non-inventor Ghofrani wrote different sections (introduction and sections on phosphodiesterase inhibitors, vasoactive therapy, treatment of pulmonary hypertension, and compiled cited literature)
  - Non-inventors Reichenberger and Grimminger wrote different section on endothelin A receptor agonists

Sources: Paper No. 29, 44-54; Paper No. 55, 25; EX2003, 2-4, 6-8.

Seeger Declaration Explains Voswinckel 2006 Authorship



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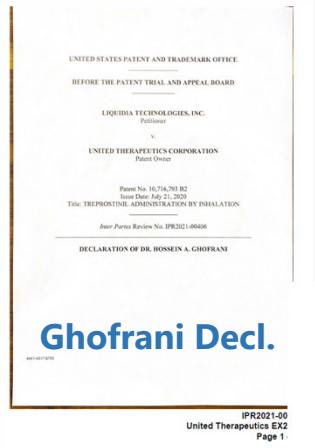
4847-7760-0219.1

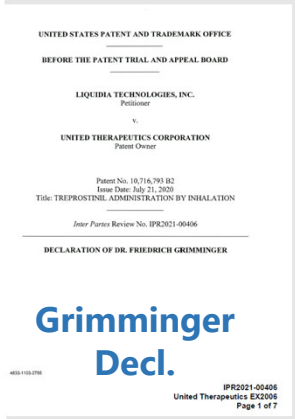
IPR2021-00406
United Therapeutics EX2003
Page 1 of 16

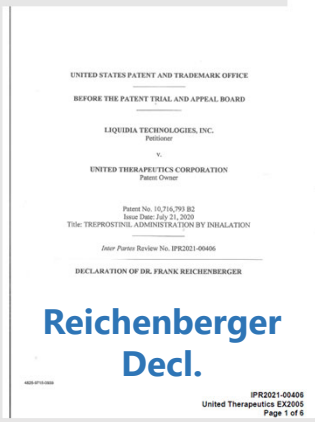
- Dr. Seeger's declaration is **unrebutted**
- Voswinckel 2006:
  - Describes inventors' own work
  - Non-inventors did not contribute to the described work
  - Non-inventors Ghofrani and Grimminger did not participate in design of clinical studies, dosing regimen, or analysis of patient results
  - Ghofrani and Grimminger performed support work and named as co-authors consistent with Giessen group's practice to acknowledge all individuals that assist with clinical trials

Sources Paper No. 29, 44-54; Paper No. 55, 25; EX2003, 8-11.

Non-inventor Author Declarations Corroborate Seeger







- Three non-inventor author declarations corroborate Seeger Declaration
- As Board observed:
  - "[A]ffidavits from the other authors disclaiming the invention are particularly strong evidence that the reference is not 'by others.'"

Paper No. 18 (Inst. Dec.) at 39 (citing *In re Katz*, 687 F.2d 450, 455-56 (CCPA 1982))

Sources: EX2004, EX2005, EX2006; Paper No. 18, 39.

ID Finds "persuasive evidence" Ghofrani & Voswinckel 2006 Not "by others"

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

Paper 18
Entered: August 11, 2021

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LIQUIDIA TECHNOLOGIES, INC.,
Petitioner,

v.

UNITED THERAPEUTICS CORPORATION,
Patent Owner.

IPR2021-00406
Patent 10,716,793 B2

Before ERICA A. FRANKLIN, CHRISTOPHER M. KAISER, and DAVID COTTA, *Administrative Patent Judges*.

KAISER, *Administrative Patent Judge*.

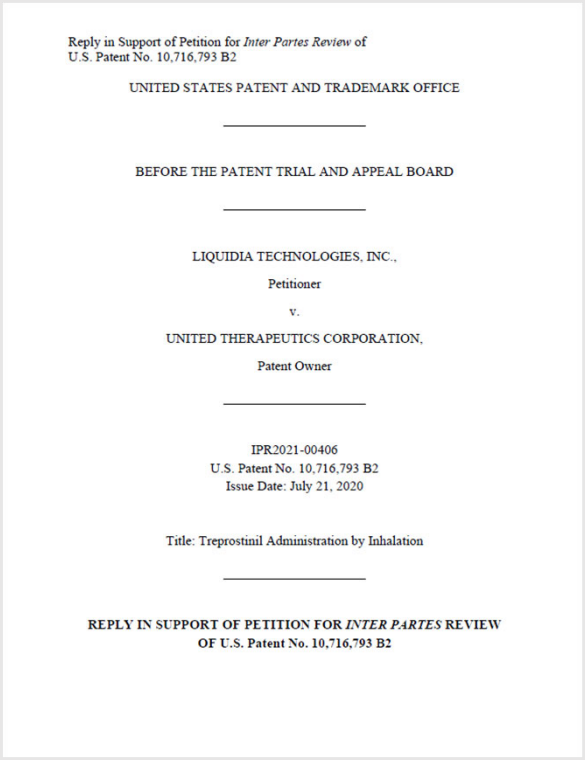
DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

Here, the present record appears to contain persuasive evidence that, despite the differences between its list of authors and the list of the inventors of the '793 patent, Ghofrani is not "by others" for purposes of § 102(a).

For the same reasons discussed above with respect to Ghofrani, we are not persuaded that the current record, without more, establishes that Petitioner has shown sufficiently that Voswinckel 2006 is "by others," but we institute on the grounds relying on Voswinckel 2006, as we are required to do under *SAS Institute*. To the extent either party disagrees with our interpretation of the law governing whether a reference is "by others," we invite such argument during trial.

Source: Paper No. 18, 39, 42-43.

Liquidia's Silence Concedes Ghofrani & Voswinckel 2006 Not "By Others"



Reply in Support of Petition for *Inter Partes Review* of
U.S. Patent No. 10,716,793 B2

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LIQUIDIA TECHNOLOGIES, INC.,
Petitioner
v.
UNITED THERAPEUTICS CORPORATION,
Patent Owner

IPR2021-00406
U.S. Patent No. 10,716,793 B2
Issue Date: July 21, 2020

Title: Treprostinil Administration by Inhalation

REPLY IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW OF U.S. Patent No. 10,716,793 B2

- Liquidia waived opportunity to depose Dr. Seeger
- Liquidia's Reply: *no evidence* on prior art status
- Liquidia's Reply: *no argument* on prior art status

Sources: Paper No. 44 (Petitioner Reply), 1-9; Paper No. 55, 2-9.

POSA

Person of Ordinary Skill in the Art (POSA)

PATENT OWNER

A person having ordinary skill in the art ("POSA") would have a graduate degree in medicine or a field relating to drug development, such as an M.D. or a Ph.D., with at least two years practical experience in either (i) the investigation or treatment of pulmonary hypertension or (ii) in the development of potential drug candidates, specifically in the delivery of drugs by inhalation.

PETITIONER

With respect to a method of treating pulmonary hypertension as of May 15, 2006, a POSA would have a medical degree with a specialty in pulmonology or cardiology, plus at least two years of experience treating patients with pulmonary hypertension as an attending, including with inhaled therapies, or equivalent degree or experience.

With respect to inhaled formulations used in the method to treat pulmonary hypertension as of May 15, 2006, a POSA would have a Ph.D. in pharmaceutical science or a related discipline like chemistry or medicinal chemistry, plus two years of experience in pharmaceutical formulations, including inhaled products, or equivalent (e.g., an M.S. in the same fields, plus 5 years of experience.

Sources: Paper No. 2, 13-14; Paper No. 29, 7-8; EX1002, ¶¶17-19; EX1004, ¶¶9-11; EX2052, ¶¶13-16; EX2053, ¶¶28-31.

Liquidia Offered No Constructions

"The petition must set forth: … (3) **How the challenged claim is to be construed**."

- 37 C.F.R. §42.1-4(b)(3)

V. CLAIM CONSTRUCTION UNDER 37 C.F.R. § 42.104(b)(3)

For purposes of resolving this IPR, Petitioner does not believe construction of any claim term is required. All terms should be given their plain and ordinary meaning in the art as of May 15, 2006. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-1313 (Fed. Cir. 2005); 37 C.F.R. § 42.100(b).

Source: Paper No. 2, 12-13.

Grounds 1 & 2:
JESC & JAHA Are Not Prior Art

Legal Principles

"'[P]ublic accessibility' has been called the touchstone in determining whether a reference constitutes a 'printed publication' .... A reference is ***publicly accessible*** 'upon a satisfactory showing that such document has been disseminated or otherwise ***made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it***.'"

Kyocera Wireless Corp. v. Int'l Trade Comm'n, 545 F.3d 1340, 1350 (Fed. Cir. 2008) (internal citations omitted)

"***[I]ndexing plays a significant role in evaluating whether a reference in a library is publicly accessible***."

Blue Calypso, LLC v. Groupon, Inc., 815 F.3d 1331, 1348 (Fed. Cir. 2016)

Source: Paper 29 at 12.

Petition Fails to Show Public Accessibility of the JESC and JAHA Abstracts

- **The Petition** argues that the JESC and JAHA Abstracts were "published" in supplements to their respective journals more than one year before priority date (citing Dr. Gonda and Dr. Hall-Ellis)
  - Dr. Gonda merely says that POSAs would have attended the conferences, and that to his recollection the journals are published in *PubMed* (EX1004, ¶¶55, 58)
  - But…
    - No evidence of what was presented at the conferences
    - No evidence that the journals/supplements/abstracts were published in *PubMed* (and in fact, these were not)

Sources: Paper No. 2, 22, 24; Paper No. 29, 10, 14, 17; Paper No. 55, 2-4, 6-9; EX1036, ¶¶ 60-67, 69-75.

Petition Fails to Show Public Accessibility of the JESC and JAHA Abstracts

- For the Petition, Dr. Hall-Ellis submits only unstamped copies of the Abstracts, and MARC records for the underlying journals (EX1036)
  - Inexplicably concludes that the Abstracts were publicly available because the MARC records were available (¶¶61, 65, 70, 74)
  - References two catalog descriptor terms "cardiology" and "heart diseases" (¶¶61, 70)
  - But…
    - NO date-stamped copies of the Supplements/Abstracts
    - NO showing that the Supplements were available to a patron
    - NO evidence of indexing of either the Abstracts or the Supplements
    - NO indication of how a POSA would reasonably find the Abstracts based on descriptors

Source: Paper No. 2, 22, 24; Paper No. 29, 10, 12-18, 17; Paper No. 55, 2-4, 6-9; EX1036, ¶¶ 60-67, 69-75.

Petition Fails to Show Public Accessibility of the JESC and JAHA Abstracts

- <u>Petition/experts fail to show public accessibility because:</u>
  - No proof that either Abstract was received and ***publicly available*** at a library or elsewhere before the priority date
  - No evidence showing how an interested POSA could locate either Abstract ***with reasonable diligence***
    - No evidence that the Supplements or the individual Abstracts were indexed or could otherwise be located through any kind of search
    - Petitioner's expert only obtained copies by providing the exact citations to the libraries

Sources: Paper No. 29, 10, 12-18; Paper No. 55, 2-3, 8-9; EX2041, ¶¶9-38; EX2043, 105:25-106:9.

Improper New Evidence and Argument on Reply

- POR pointed out the deficiencies in the Petition evidence
- In Reply (Paper 44), Petitioner attempted to submit **NEW** evidence and arguments alleging that:
  - Abstracts were "publicly presented" at their respective conferences
  - Each Abstract cited in another journal article ("research aids")
  - Supplements were by an "established publisher"/alleged on-line availability of the Supplements/Abstracts
  - Date-stamped copies of each Supplement, now with reference to alleged indexes within the Supplements

Sources: Paper No. 29, 10, 12-18; Paper No. 44 (Pet. Reply), 2-9; Paper No. 46 (PO Obj. To Reply Evidence).

Liquidia's New Reply Evidence is Improper

- Petitioner's Reply arguments and evidence are improper (Sur-Reply at 3):
  - *Intelligent Bio-Systems v. Illumina Cambridge*, 821 F.3d 1359, 1369 (Fed. Cir. 2016) ("It is of the utmost importance that petitioners in the IPR proceedings adhere to the requirement that the initial petition identify 'with particularity' the 'evidence that supports the grounds for the challenge to each claim.' 35 U.S.C. § 312(a)(3).")
  - *Trial Practice Guide*, 74 ("It is also improper for a reply to present new evidence (including new expert testimony) that could have been presented in a prior filing.")
- Petitioner's attempt to submit date-stamped copies as Supplemental Information denied for failure to show it could not have been presented earlier (Paper 30, 3-5)
  - Petitioner did not even attempt to justify late filing in its Reply
- Patent Owner sought permission to file evidence responsive to Petitioner's Reply evidence, but was prevented from doing so (Paper 50)

Sources: Paper Nos. 30 (Order Deny Pet. Req. Submit Suppl. Info.); 47 (PO Id. Non-Responsive Evid.); 50 (Order); 55, 3.

Petitioner's Reply Evidence Fails to Establish Public Accessibility

- ***Even if considered, petitioner's reply evidence fails***
- Petitioner presented no evidence from the JESC or JAHA conferences
  - NO testimony from anyone who attended the conferences
  - NO evidence that the Abstracts were displayed or recited
  - NO evidence that the Abstracts were distributed (e.g., no evidence of "Abstract books")

Source: Paper No. 55, 3-5.

"Research Aid" Evidence Does Not Prove Prior Art Status

- ***Even if considered, the "research aids" both fail to establish public accessibility***
  - As pure research aide, Ghofrani and Sulica not shown to have published before May 15, 2005—public accessibility after this date allows for their disqualification as not "by another"
  - Also, no evidence that these authors were able to independently find the Abstracts, because the authors of both Ghofrani and Sulica were connected to the Giessen inventor group:
    - Ghofrani: Authors included Voswinckel and Seeger
    - Sulica: Principal Investigator in TRIUMPH study group that participated in the clinical trial reported in the Voswinckel publications

Sources: Paper No. 55, 9-11; EX2003, ¶27; EX2061, ¶¶12-13; EX2071, ¶¶6-8; EX2094, 30:19-31:19, 75-76.

No Evidence of On-Line Availability of JESC or JAHA

AHA Archive listing of *Circulation* Supplements:

December 14, 2004

Prevention of Venous Thromboembolism
Volume 110, Issue 24 Supplement; December 14, 2004

September 14, 2004

Cardiovascular Surgery Supplement 2004
Volume 110, Issue 14 Supplement; September 14, 2004

August 31, 2004

Treatment of Venous Thromboembolism
Volume 110, Issue 9 Supplement; August 31, 2004

https://www.ahajournals.org/circ/supplements

EX2044, 5

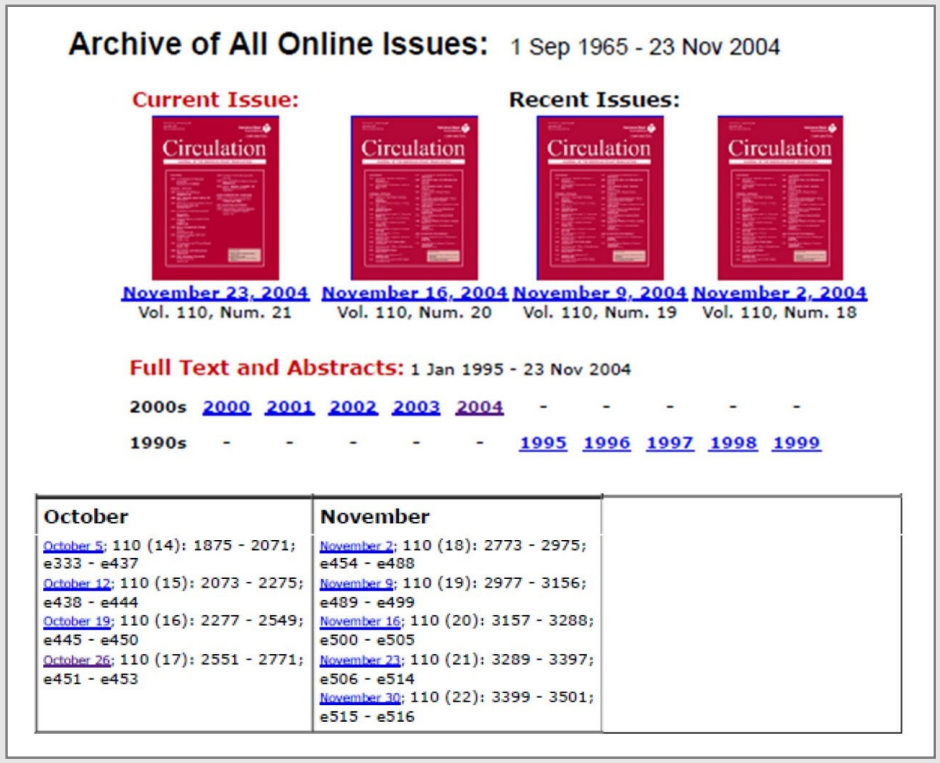
Patent Owner's Expert, Ms. Wyman:

- NO listing for Volume 110, Issue 17 Supplement (Oct. 2004)
- Keyword searches also do not retrieve the JAHA Supplement
- No copy of the Supplement could be found on-line

EX2041,¶¶ 12-15

Sources: Paper No. 29, 16; EX2041, ¶¶12, 15; EX2044, 5.

No Evidence of On-Line Availability of JESC or JAHA



Archive of All Online Issues: 1 Sep 1965 - 23 Nov 2004

Current Issue: **Recent Issues:**

November 23, 2004 Vol. 110, Num. 21 | November 16, 2004 Vol. 110, Num. 20 | November 9, 2004 Vol. 110, Num. 19 | November 2, 2004 Vol. 110, Num. 18

Full Text and Abstracts: 1 Jan 1995 - 23 Nov 2004

2000s 2000 2001 2002 2003 2004 - - - - -

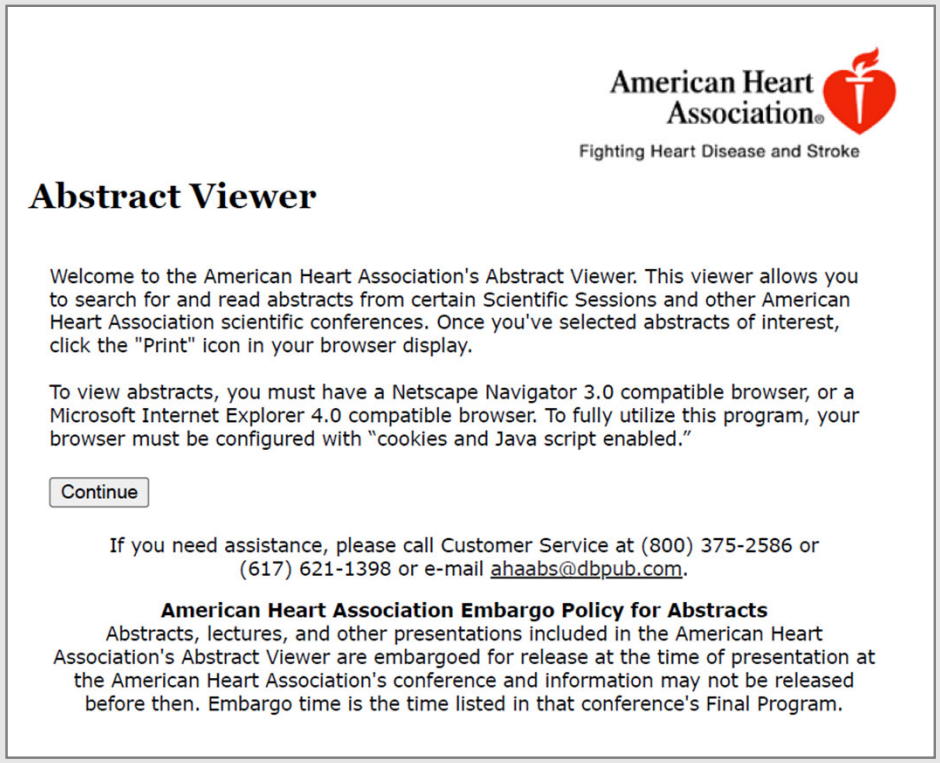
1990s - - - - - 1995 1996 1997 1998 1999

October	November
October 5; 110 (14): 1875 - 2071; e333 - e437 October 12; 110 (15): 2073 - 2275; e438 - e444 October 19; 110 (16): 2277 - 2549; e445 - e450 October 26; 110 (17): 2551 - 2771; e451 - e453	November 2; 110 (18): 2773 - 2975; e454 - e488 November 9; 110 (19): 2977 - 3156; e489 - e499 November 16; 110 (20): 3157 - 3288; e500 - e505 November 23; 110 (21): 3289 - 3397; e506 - e514 November 30; 110 (22): 3399 - 3501; e515 - e516

- NO evidence that either Abstract, or the Supplements as a whole, were indexed or available on-line:
  - EX1114: Wayback machine archive of *Circulation* (i.e., JAHA Abstract) ***does not*** include the JAHA Supplement or the abstracts within
  - Hall-Ellis admits she did not locate the JAHA Abstract via this website (EX2094, 50:11-56:22)

Sources: Paper No. 55, 6-7; Paper No. 66 (Motion to Exclude), 10-12; EX1112, ¶39 (citing EX1014); EX1114; EX2094, 50:11-56:22.

No Evidence of On-Line Availability of JESC or JAHA



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Abstracts, lectures, and other presentations included in the American Heart Association's Abstract Viewer are embargoed for release at the time of presentation at the American Heart Association's conference and information may not be released before then. Embargo time is the time listed in that conference's Final Program.

- Same lack of evidence as to this page:
  - No evidence that this Abstract Viewer encompassed the JAHA Abstract
  - Dr. Hall-Ellis admits she did not locate the JAHA Abstract via this website (EX2094, 50:11-51:10)
  - Patent Owner precluded from introducing sur-reply evidence to affirmatively prove that the JAHA abstract was not so accessible

Sources: Paper No. 50; Paper No. 55, 6-7; Paper No. 66, 10-13; EX1112 ¶39 (citing EX1014); EX2094, 50:11-51:10.

No Evidence of On-Line Availability of JESC or JAHA

152 Abstracts from the 2004 Scientific Sessions of the American Heart Association. November 7-10, 2004, New Orleans, Louisiana, USA.
[No authors listed]
Circulation. 2004 Oct 26;110(17 Suppl):III1-835.
PMID: 16082756 No abstract available.

EX1017 at 17 (PubMed "search results")

☐ 34 Inhaled treprostinil is a potent pulmonary vasodilator in severe pulmonary hypertension
Voswinckel, R; Kohstall, MG; (...); Olschewski, H
ESC Congress 2004
Aug-sep 2004 | EUROPEAN HEART JOURNAL 25 , pp.22-22

EX1020 at 5 (Web of Science "search results")

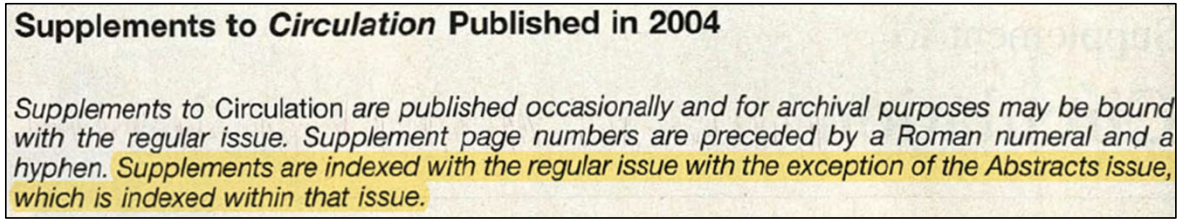
- NO evidence that either Abstract, or the Supplements as a whole, were available on-line:
  - NEITHER result shows that the actual Abstracts were available
  - NEITHER result shows search results as of 2006 or before

See EX2094 at 24:10-26:6, 27:11-28:9, 41:18-42:20

Sources: Paper No. 55, 6-7; Paper No. 66, 13-14.

JESC and JAHA Supplements and Abstracts Lack Meaningful Indexing

- ***Both Abstracts are obscure*** – not indexed on standard databases like Ovid, PubMed, MEDLINE, Index Medicus, and Chemical Abstracts (EX2041, ¶¶5, 16-17, 37)
  - These are the indexes Dr. Hall-Ellis said a POSA would turn to in 2004-2005 (EX2043, 41:1-42:4; 242:11-243:18)
  - Consistent with what the JAHA Supplement says about indexing:



Supplements to *Circulation* Published in 2004

Supplements to Circulation *are published occasionally and for archival purposes may be bound with the regular issue. Supplement page numbers are preceded by a Roman numeral and a hyphen. Supplements are indexed with the regular issue with the exception of the Abstracts issue, which is indexed within that issue.*

EX1095 at 12

- Without being indexed outside of the Supplements themselves, a POSA would never know what abstracts exist or what citations to ask for from a library

Sources: Paper 29, 16; Paper 55 at 7-10; EX2071, ¶¶6-8; EX2003, ¶27; EX2061, ¶¶12-13.

Petitioner Fails to Establish Accessibility of the Supplements

- Hall-Ellis relies on British Librarian statement (EX1116) to claim that the JAHA Supplement was "available for public use"
- **BUT** Patent Owner's impeachment exhibit (a different British Librarian statement) indicates that it wasn't available as a whole:

> 2. Customers cannot normally request a copy of an entire journal issue. If a customer requests a copy of a single article/conference abstract, our Customer Services staff use our catalogue Explore The British Library http://explore.bl.uk to identify the journal's shelfmark in our Document Supply collection. From this they can ascertain its location in our storage facility. The relevant issue is then fetched from the shelf, and the article is identified and copied. The customer may either stipulate the article's title and/or other bibliographic details, or they may stipulate a range of page numbers in the journal issue, or (preferably) both. If there is any uncertainty about which pages in a journal issue the customer requires, our staff may contact the customer for further clarification.
>
> EX2094, 64 (emphasis added)

- The only possible "indexes" were within the Supplements themselves, but evidence suggests that the entire Supplements couldn't be checked out

Sources: Paper No. 44, 8-9; Paper No. 55, 6-8; EX1116; Depo. Ex. 2092 of Hall-Ellis 2nd Deposition (EX2094, 64).

JESC & JAHA Are Not Prior Art – Summary

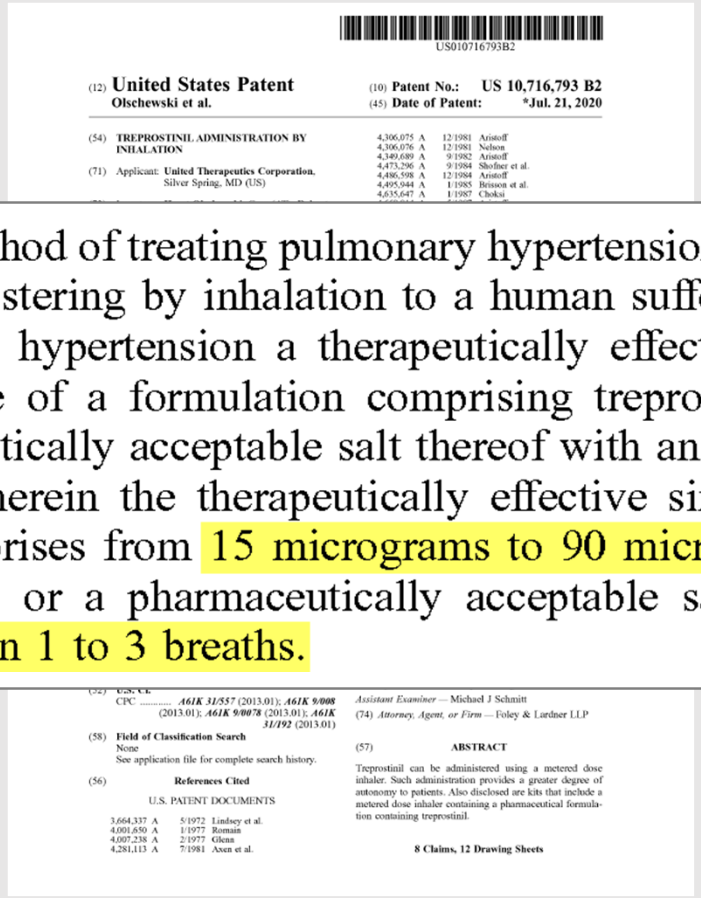
- Petition does not establish any meaningful indexing of the Supplements, or of the Abstracts themselves, or any date of public accessibility for either
- Although not in the Petition, even if the Supplements were received by libraries before priority date, no evidence that the Supplements were available in their entirety to POSAs
- Without the entire JESC and JAHA Supplements, no way for a POSA to locate the individual Abstracts
  - Petitioner fails to prove that the Abstracts were "**made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence[] can locate it**"

Kyocera Wireless Corp. v. Int'l Trade Comm'n, 545 F.3d 1340, 1350 (Fed. Cir. 2008) (citations omitted).

Sources: Paper No. 29, 12, 16; Paper No. 55, 6-11.

Grounds 1 & 2: No Reference Discloses The Claimed Dose

Claim 1 Requires A Dose Of 15-90 µg



US010716793B2

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

(10) **Patent No.: US 10,716,793 B2**
(45) **Date of Patent: *Jul. 21, 2020**

(54) **TREPROSTINIL ADMINISTRATION BY INHALATION**

(71) Applicant: **United Therapeutics Corporation**, Silver Spring, MD (US)

4,306,075 A 12/1981 Aristoff
4,306,076 A 12/1981 Nelson
4,349,689 A 9/1982 Aristoff
4,473,296 A 9/1984 Shofner et al.
4,486,598 A 12/1984 Aristoff
4,495,944 A 1/1985 Brisson et al.
4,635,647 A 1/1987 Choksi

1. A method of treating pulmonary hypertension comprising administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof with an inhalation device, wherein the therapeutically effective single event dose comprises from 15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 3 breaths.

CPC ***A61K 31/557*** (2013.01); ***A61K 9/008*** (2013.01); ***A61K 9/0078*** (2013.01); ***A61K 31/192*** (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,664,337 A 5/1972 Lindsey et al.
4,001,650 A 1/1977 Romain
4,007,238 A 2/1977 Glenn
4,281,113 A 7/1981 Axen et al.

Assistant Examiner — Michael J Schmitt
(74) *Attorney, Agent, or Firm* — Foley & Lardner LLP

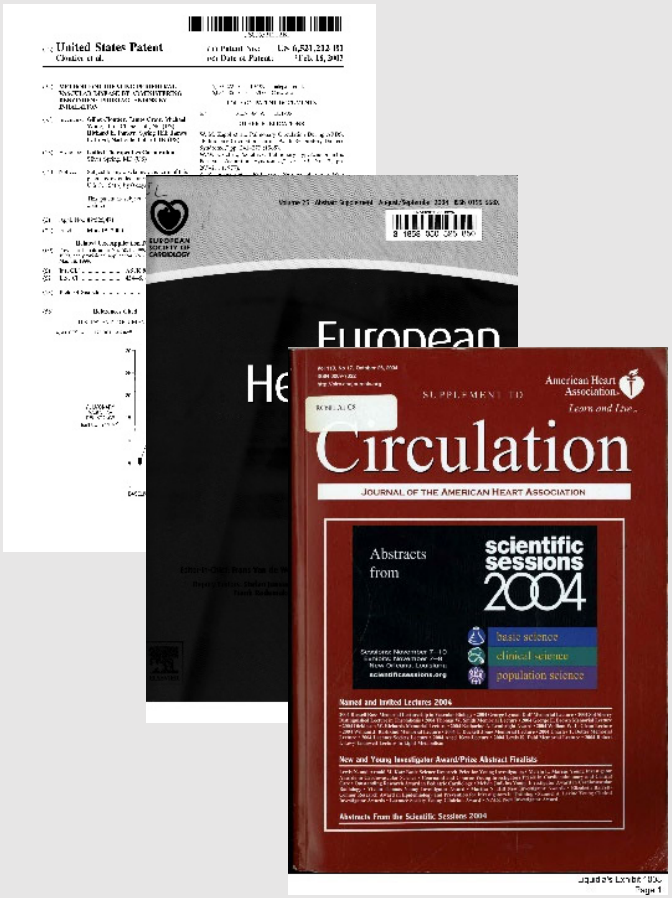
(57) **ABSTRACT**

Treprostinil can be administered using a metered dose inhaler. Such administration provides a greater degree of autonomy to patients. Also disclosed are kits that include a metered dose inhaler containing a pharmaceutical formulation containing treprostinil.

8 Claims, 12 Drawing Sheets

Source: EX1001, claim 1.

Liquidia's References Do Not Disclose the Claimed 15-90 µg Dose

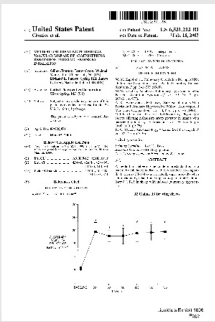


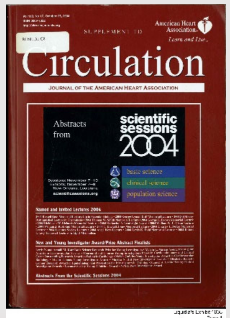
- Proper obviousness inquiry: do references disclose or teach 15-90 µg dose?
- Answer: no

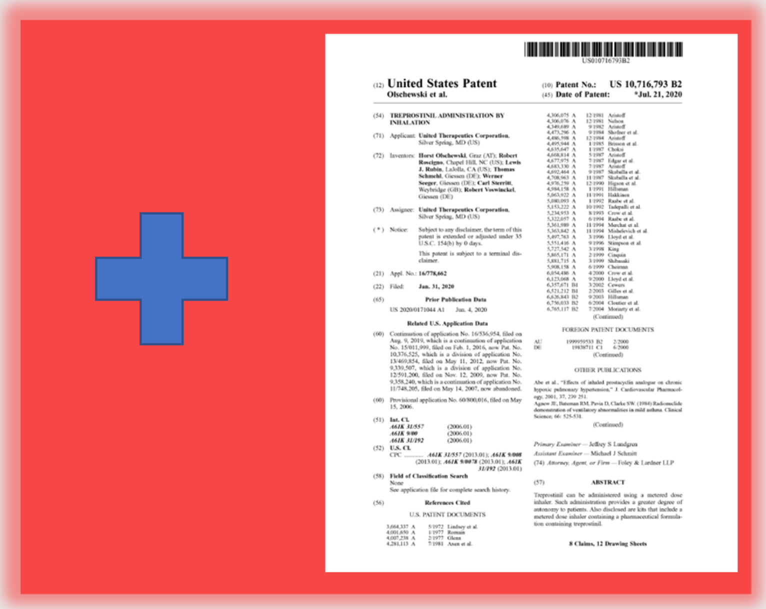
<u>Only disclosure of 15-90 µg dose is the '793 patent</u>

Sources: Paper No. 13 (PO Preliminary Response), 43; Paper No. 29, 18-22.

Hindsight







Dr. Hill:

Q. So about a year ago when you started your analysis, you had the '793 patent in your hands, correct?

A. Yes.

Q. And you had materials that you had received from counsel, correct?

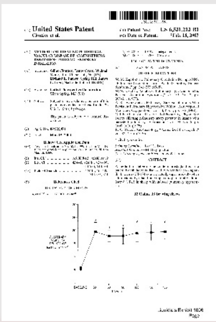
A. That is correct.

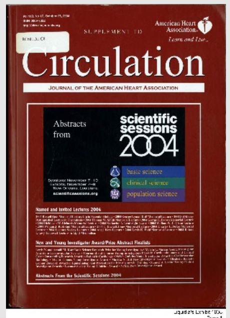
Q. So you knew when you started your analysis on the claims of the '793 patent – what they said, correct?

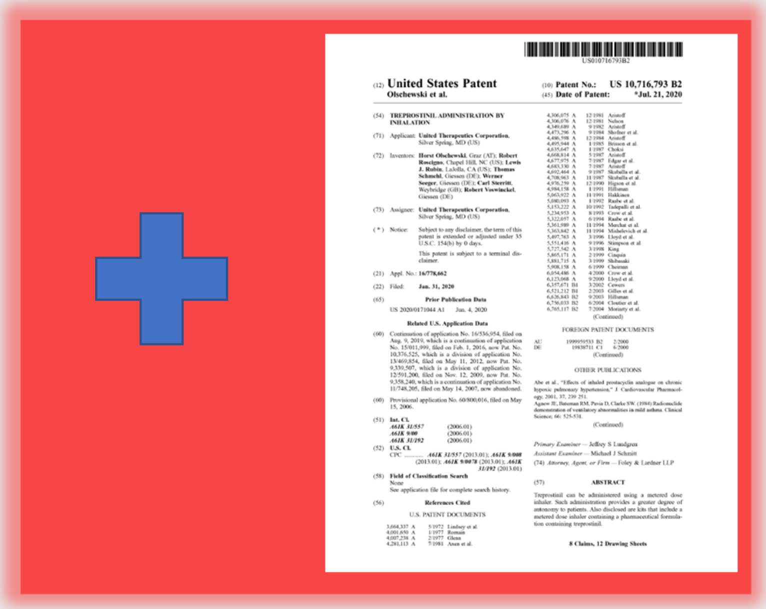
A. Correct.

Source: EX2055, 35:25-36:10.

Hindsight





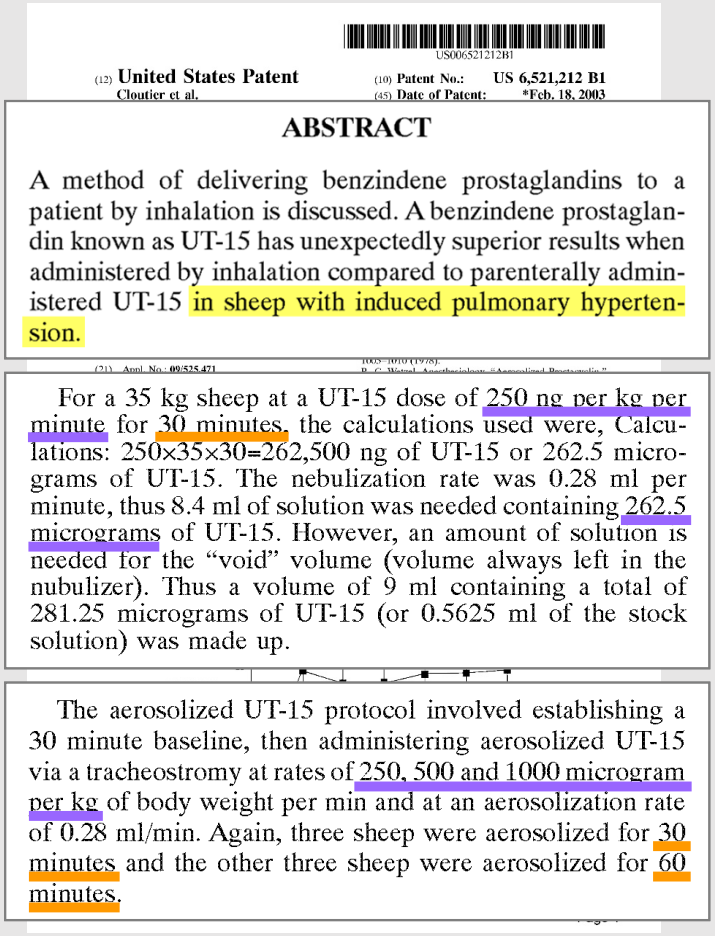


Dr. Gonda:

Q. And is it fair to say that to analyze obviousness, you first reviewed the 793 patent and then compared that to the prior art.

A. Yes. The process as far as I recall was to look at the 793 and then compare that patent to the prior art.

The '212 Patent Discloses Rates (Not Doses) For Sheep (Not Humans)



US006521212B1

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

(10) Patent No.: US 6,521,212 B1
(45) Date of Patent: *Feb. 18, 2003

ABSTRACT

A method of delivering benzindene prostaglandins to a patient by inhalation is discussed. A benzindene prostaglandin known as UT-15 has unexpectedly superior results when administered by inhalation compared to parenterally administered UT-15 in sheep with induced pulmonary hypertension.

For a 35 kg sheep at a UT-15 dose of 250 ng per kg per minute for 30 minutes, the calculations used were, Calculations: 250×35×30=262,500 ng of UT-15 or 262.5 micrograms of UT-15. The nebulization rate was 0.28 ml per minute, thus 8.4 ml of solution was needed containing 262.5 micrograms of UT-15. However, an amount of solution is needed for the "void" volume (volume always left in the nubulizer). Thus a volume of 9 ml containing a total of 281.25 micrograms of UT-15 (or 0.5625 ml of the stock solution) was made up.

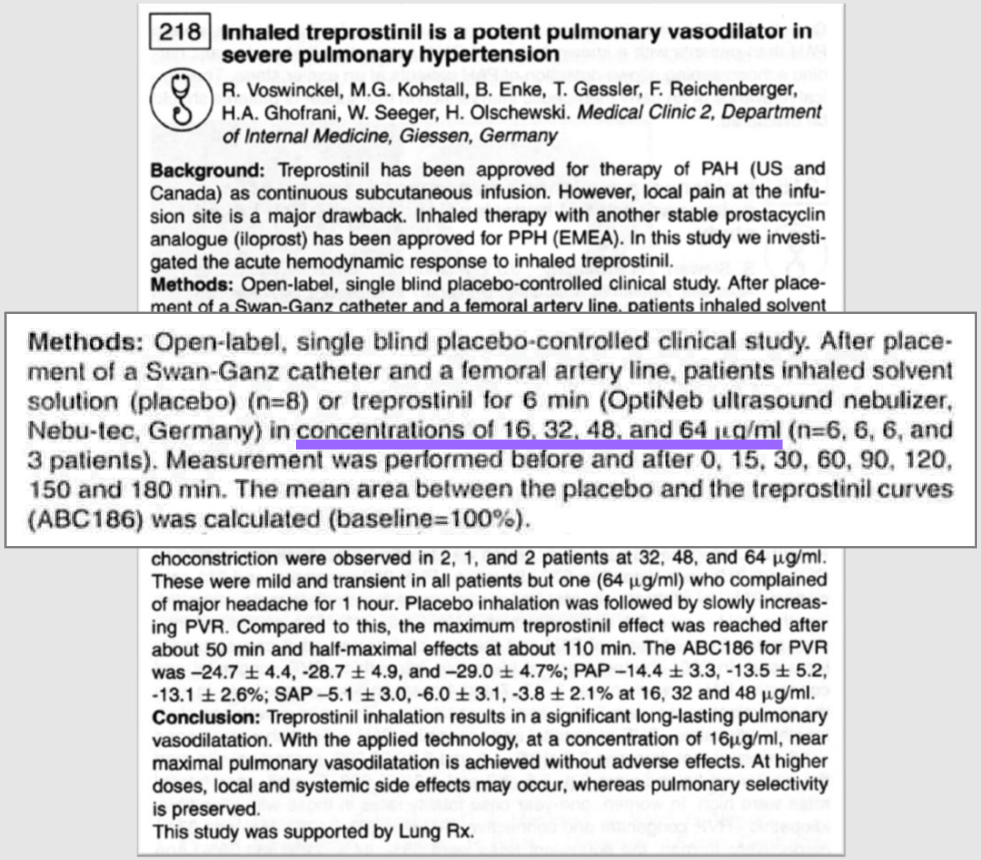
The aerosolized UT-15 protocol involved establishing a 30 minute baseline, then administering aerosolized UT-15 via a tracheostromy at rates of 250, 500 and 1000 microgram per kg of body weight per min and at an aerosolization rate of 0.28 ml/min. Again, three sheep were aerosolized for 30 minutes and the other three sheep were aerosolized for 60 minutes.

'212 patent does not teach the claimed dose:

- Chemically induced PH
- Sheep, not humans
- Rates, not doses
- 30-90 minutes, not 1-3 breaths
- Liquidia's cited range: PVD, not PH
- Board agreed it does not teach claimed dose (ID, 26-27)

Sources: Paper No. 55, 17-19; EX1006; EX2052, ¶¶ 58, 62.

JESC Discloses Concentration (Not Dose)



218 **Inhaled treprostinil is a potent pulmonary vasodilator in severe pulmonary hypertension**

R. Voswinckel, M.G. Kohstall, B. Enke, T. Gessler, F. Reichenberger, H.A. Ghofrani, W. Seeger, H. Olschewski. *Medical Clinic 2, Department of Internal Medicine, Giessen, Germany*

Background: Treprostinil has been approved for therapy of PAH (US and Canada) as continuous subcutaneous infusion. However, local pain at the infusion site is a major drawback. Inhaled therapy with another stable prostacyclin analogue (iloprost) has been approved for PPH (EMEA). In this study we investigated the acute hemodynamic response to inhaled treprostinil.

Methods: Open-label, single blind placebo-controlled clinical study. After placement of a Swan-Ganz catheter and a femoral artery line, patients inhaled solvent solution (placebo) (n=8) or treprostinil for 6 min (OptiNeb ultrasound nebulizer, Nebu-tec, Germany) in concentrations of 16, 32, 48, and 64 µg/ml (n=6, 6, 6, and 3 patients). Measurement was performed before and after 0, 15, 30, 60, 90, 120, 150 and 180 min. The mean area between the placebo and the treprostinil curves (ABC186) was calculated (baseline=100%).

choconstriction were observed in 2, 1, and 2 patients at 32, 48, and 64 µg/ml. These were mild and transient in all patients but one (64 µg/ml) who complained of major headache for 1 hour. Placebo inhalation was followed by slowly increasing PVR. Compared to this, the maximum treprostinil effect was reached after about 50 min and half-maximal effects at about 110 min. The ABC186 for PVR was –24.7 ± 4.4, -28.7 ± 4.9, and –29.0 ± 4.7%; PAP –14.4 ± 3.3, -13.5 ± 5.2, -13.1 ± 2.6%; SAP –5.1 ± 3.0, -6.0 ± 3.1, -3.8 ± 2.1% at 16, 32 and 48 µg/ml.

Conclusion: Treprostinil inhalation results in a significant long-lasting pulmonary vasodilatation. With the applied technology, at a concentration of 16µg/ml, near maximal pulmonary vasodilatation is achieved without adverse effects. At higher doses, local and systemic side effects may occur, whereas pulmonary selectivity is preserved.

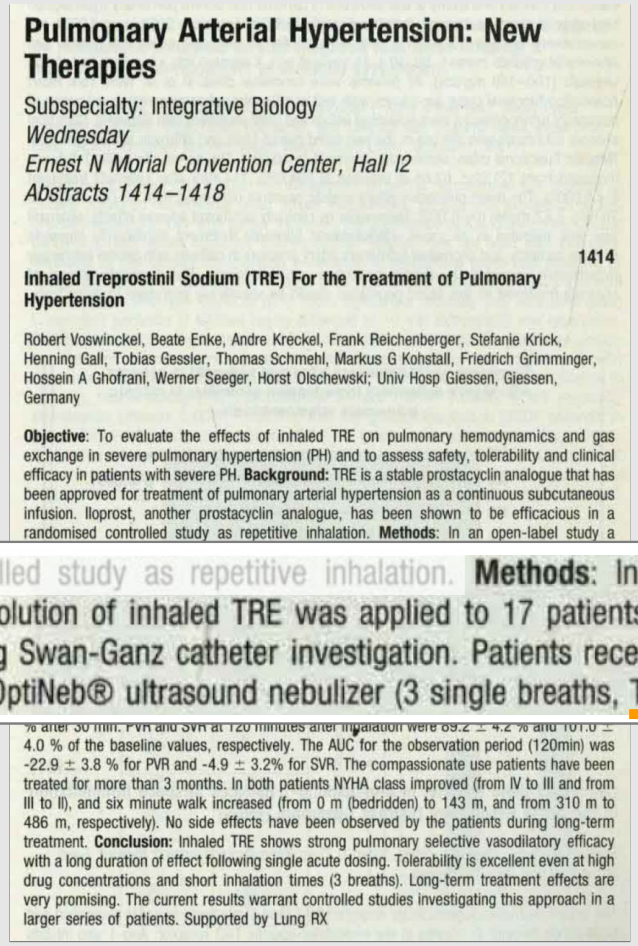
This study was supported by Lung Rx.

JESC does not teach the claimed dose:

- Concentrations of 16, 32, 48, 64 µg/mL
- Pre-aerosolized concentration of solution put into device
- Continuous inhalation for 6 minutes, not 1-3 breaths
- No disclosure of µg of treprostinil delivered to patient

Sources: Paper No. 29, 20-21; EX1007; EX2052, ¶¶ 65-67.

Voswinckel JAHA Discloses Concentration (Not Dose)



Pulmonary Arterial Hypertension: New Therapies

Subspecialty: Integrative Biology
Wednesday
Ernest N Morial Convention Center, Hall I2
Abstracts 1414–1418

1414

Inhaled Treprostinil Sodium (TRE) For the Treatment of Pulmonary Hypertension

Robert Voswinckel, Beate Enke, Andre Kreckel, Frank Reichenberger, Stefanie Krick, Henning Gall, Tobias Gessler, Thomas Schmehl, Markus G Kohstall, Friedrich Grimminger, Hossein A Ghofrani, Werner Seeger, Horst Olschewski; Univ Hosp Giessen, Giessen, Germany

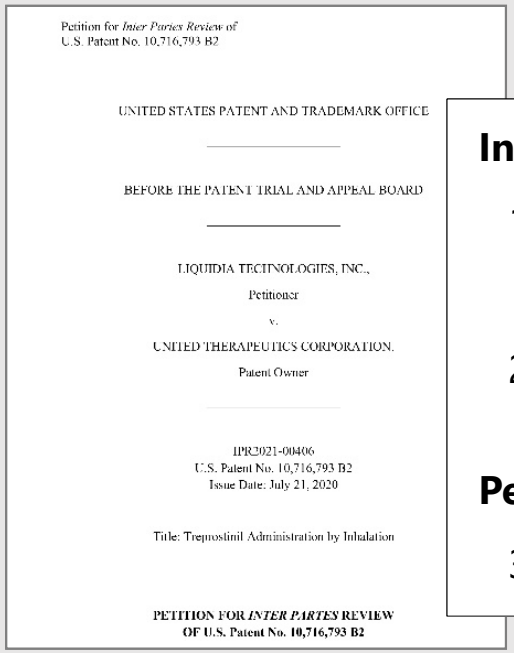
Objective: To evaluate the effects of inhaled TRE on pulmonary hemodynamics and gas exchange in severe pulmonary hypertension (PH) and to assess safety, tolerability and clinical efficacy in patients with severe PH. **Background:** TRE is a stable prostacyclin analogue that has been approved for treatment of pulmonary arterial hypertension as a continuous subcutaneous infusion. Iloprost, another prostacyclin analogue, has been shown to be efficacious in a randomised controlled study as repetitive inhalation. **Methods**: In an open-label study a preservative free solution of inhaled TRE was applied to 17 patients with severe pulmonary hypertension during Swan-Ganz catheter investigation. Patients received a TRE inhalation by use of the pulsed OptiNeb® ultrasound nebulizer (3 single breaths, TRE solution 600 µg/ml). % after 30 min. PVR and SVR at 120 minutes after inhalation were 89.2 ± 4.2 % and 101.0 ± 4.0 % of the baseline values, respectively. The AUC for the observation period (120min) was -22.9 ± 3.8 % for PVR and -4.9 ± 3.2% for SVR. The compassionate use patients have been treated for more than 3 months. In both patients NYHA class improved (from IV to III and from III to II), and six minute walk increased (from 0 m (bedridden) to 143 m, and from 310 m to 486 m, respectively). No side effects have been observed by the patients during long-term treatment. **Conclusion:** Inhaled TRE shows strong pulmonary selective vasodilatory efficacy with a long duration of effect following single acute dosing. Tolerability is excellent even at high drug concentrations and short inhalation times (3 breaths). Long-term treatment effects are very promising. The current results warrant controlled studies investigating this approach in a larger series of patients. Supported by Lung RX

JAHA does not teach the claimed dose:

- Concentration of 600 µg/mL
- Pre-aerosolized concentration
- No disclosure of µg of treprostinil delivered to patient

Sources: Paper No. 29, 22; EX1008; EX2052, ¶72, et seq.

Liquidia Uses Flawed Calculations To Backfill Missing Dose



Petition for *Inter Partes Review* of
U.S. Patent No. 10,716,793 B2

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LIQUIDIA TECHNOLOGIES, INC.,

Petitioner

v.

UNITED THERAPEUTICS CORPORATION,

Patent Owner

IPR2021-00406
U.S. Patent No. 10,716,793 B2
Issue Date: July 21, 2020

Title: Treprostinil Administration by Inhalation

PETITION FOR *INTER PARTES* REVIEW OF U.S. Patent No. 10,716,793 B2

Institution Decision recognized two calculations:

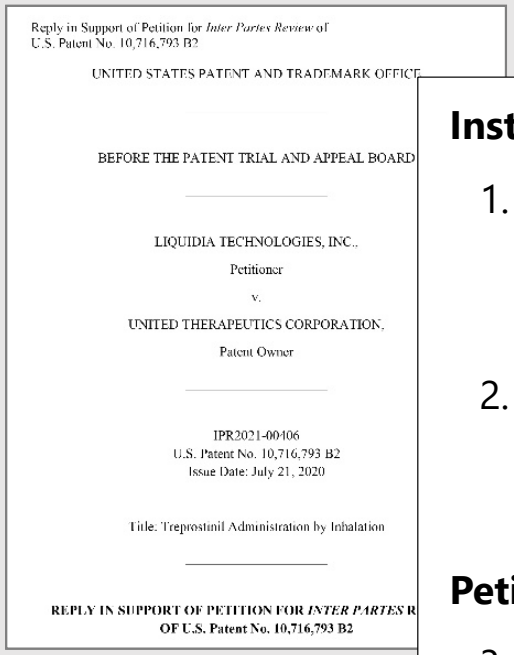
1. [JESC concentrations] * [assumed volumes]
   - "[C]onfirmation" of volumes from [OptiNeb manual rate] * [time]
2. [Remodulin IV dosing] * [alleged '212 patent 10-50% conversion rate], as "confirmation"

Petition Footnote 13 asserts PVD doses are "equally possible" (?):

3. ['212 patent PVD daily range 2.5 µg-125 mg]

Sources: Paper No. 2, 39-40; Paper No. 18, 28-30; Paper No. 44, 12-14.

Liquidia Uses Flawed Calculations To Backfill Missing Dose


Reply in Support of Petition for *Inter Partes Review* of
U.S. Patent No. 10,716,793 B2

UNITED STATES PATENT AND TRADEMARK OFFICE

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IPR2021-00406
U.S. Patent No. 10,716,793 B2
Issue Date: July 21, 2020

Title: Treprostinil Administration by Inhalation

REPLY IN SUPPORT OF PETITION FOR *INTER PARTES* R
OF U.S. Patent No. 10,716,793 B2

Reply added new and revised arguments

Institution Decision recognized two calculations:

1. [JESC concentrations] * [assumed volumes] * efficiency
   - "[C]onfirmation" of volumes from [OptiNeb manual rate and additional references] * [time]
2. [Remodulin IV dosing] * [alleged '212 patent 10-50% conversion rate], as "confirmation"
   - Heavier patients, new formulas, up-titrated dose rates, divides by 4

Petition Footnote 13 asserts PVD doses are "equally possible" (?):

3. ['212 patent PVD daily range 2.5 µg-125 mg] divided by 4

Sources: Paper No. 2, 39-40; Paper No. 18, 28-30; Paper No. 44, 12-14.

Flawed Calculation #1 - JESC

Dose Is Delivered To Patient

Dr. Waxman

[8] A POSA would understand that a claimed single event dose of 15 micrograms to 90 micrograms means the dose delivered to the patient – not the amount of the starting solution.

Dr. Hill

In the context of the '793 Patent, the claimed "single event dose" of 15 to 90 µg refers to the dose emitted at the mouthpiece.

Dr. Gonda

13. A POSA in May 2006 in the field of inhaled formulations would understand that a "dose" that is "delivered" as used in the '793 Patent to mean the dose delivered to the mouthpiece and inhaled by a patient.

Sources: EX2052, ¶65, n.8; EX1106, ¶39; EX1107, ¶13.

Dr. Waxman: POSA Could Not Calculate Delivered Dose From JESC

Based on my knowledge and experience, a POSA would also need to account for the gas flow and pressure, fill and dead volumes, gas density, and humidity and temperature conditions, breathing pattern and device interface, among other things. EX2029-EX2031. None of these parameters are disclosed in Voswinckel JESC and, in my opinion, a POSA would be unable to determine the actual single event dose administered in the described study described in Voswinckel JESC. Even if a POSA were to attempt a rough estimate of an administered dose, the range would be very broad and unreliable.

[7] I note that a POSA would not likely rely on abstracts such as Voswinckel JESC and Voswinckel JAHA because conference abstracts are not peer-reviewed to the same rigor as published journal articles, and further often report preliminary data which may or may not translate into actual results.

- POSA could not calculate dose because too many variables

- POSA would not rely on JESC to calculate a dose

Sources: EX2052, ¶¶ 65, n.7, 66.

Dr. McConville: POSA Could Not Calculate Delivered Dose From JESC

Unknowns:

- Formulation
  - Solvent
  - Excipients
- Device
  - Model Number
  - No characterization data – only know it was ultrasonic
- Nebulizer use
  - Fill volume
  - Residual volume
  - Frequency
  - MMAD
  - Output rate
  - Efficiency
- Patient Factors
  - Number breaths
  - Breath rate
  - Breath depth

- POSA could not calculate dose because there are too many variables

Sources: Paper No. 29, 21, 23-37; EX2053, ¶¶55-57.

Petition Presents Unrealistic View Of Dose Calculations

Hill's First Calculation

Volume (mL)

× Concentration (µg/mL)

Alleged "Confirmation"

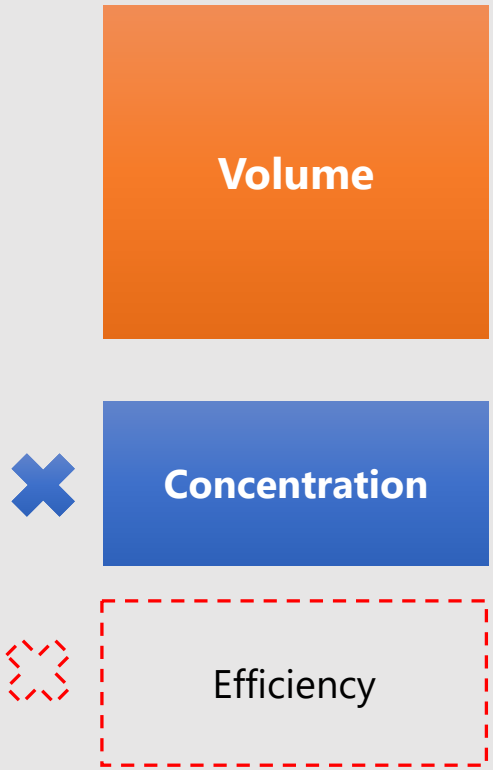
Rate (mL/min)

× Time (min)

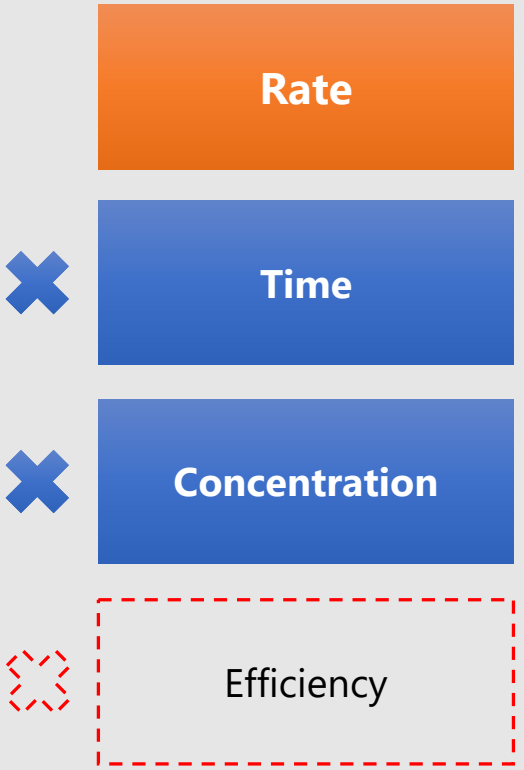
× Concentration (µg/mL)

Sources: Paper No. 2; EX1002; EX1106.

Liquidia's Variations Of Calculation #1 Are Flawed



- References do not disclose volume
- References do not disclose rate
- Petition omitted efficiency
- References do not disclose efficiency



Sources: Paper No. 2; EX1002; EX1106.

1 **Volume Flaws**

2 Rate Flaws

3 Efficiency Flaws

Calculation #1: Assumptions About Nebulizer Volume In JESC Are Flawed

Dr. Hill cites:

- Unspecified experience (with other drugs)
- Gonda Decl. (EX1004, ¶56), which relies on three drug labels for alleged 1-5 mL range
- "[C]onfirm[ation]" from OptiNeb Manual, EX1037
  - UTC objected to EX1037
  - Calculation: [0.6 mL/min rate] * [6 min] = 3.6 mL

All flawed

Sources: Paper No. 29, 25; EX1002, ¶65, 67; EX1004, ¶56; EX1037.

Calculation #1: Dr. Hill's Prescribed Volumes Are Unrelated

Dr. Waxman:

69. *Third,* even if a POSA could determine the dosage based on the simplified formula used by Dr. Hill in his declaration, Dr. Gonda's assertion that "[a] POSA would have known that nebulizers conventionally deliver between 1 and 5 mL dose" (para 56 and n. 4) and Dr. Hill's assertion that he had in his own practice "prescribed volumes of at[sic] least 1 mL for inhalation therapy using nebulizers" (paragraph 65) is irrelevant, because neither experts' statements take into account the particular drug to be administered or the concentration of that drug solution. For example, Dr. Hill stated that his experience delivering 1 mL or more of solution was based upon different indications and drugs. EX2055 (Hill Dep. Tr.), 146:16-23 (identifying bronchodilators for asthma/COPD, inhaled corticosteroids, and anticholinergics as "the main things I would have nebulized"). Dr. Hill did not

Dr. Hill:

Q. What products did you prescribe for use in nebulizers before 2006 in volumes of at least 1 milliliter, if you recall?

A. Well, certainly bronchodilators for treatment of asthma of COPD, inhaled corticosteroids, anticholinergics such as Ipratropium. I think that would be the main things I would have nebulized.

- **Not** treprostinil
- **Not** pulmonary hypertension

Sources: Paper No. 29, 23-27; Paper No. 64 (UTC Observ. on Dep. of Dr. Hill), 1; EX2052, ¶69; EX2055, 146:16-23.

Calculation #1: Dr. Hill's Testimony Is Vague

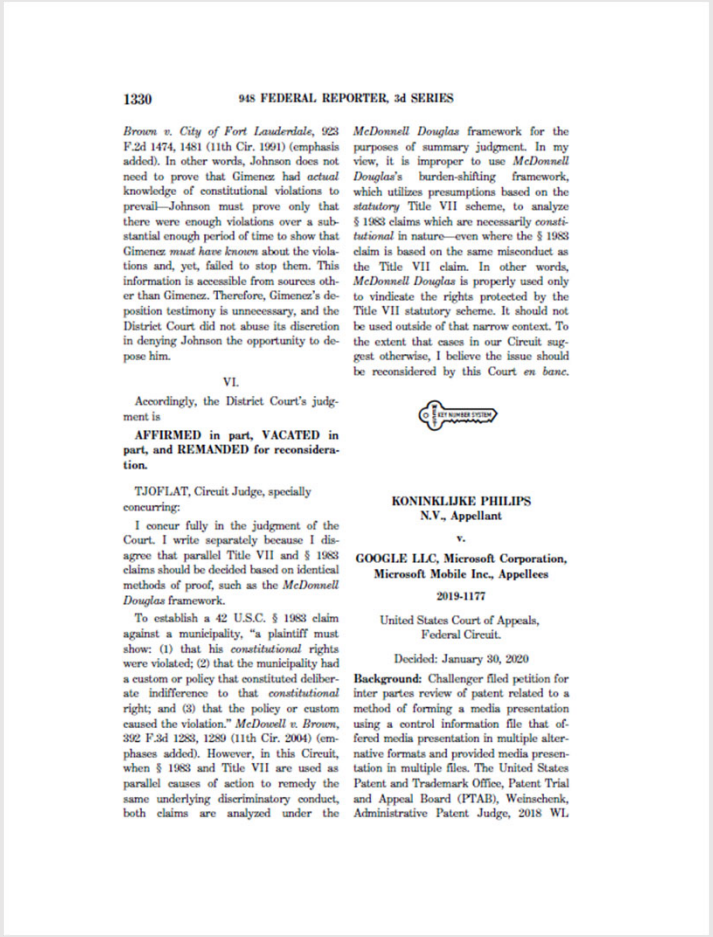
Dr. Hill:

65. A POSA in 2006 reading Voswinckel JESC would assume that the study used a sufficient volume of treprostinil solution for 6 minutes of delivery which a POSA would understand to be at least 1 mL because nebulizers at the time were known to nebulize (i.e. aerosolize liquid) at least that volume. Ex. 1004 (Gonda Decl.) at paragraph 56. In my own practice, I prescribed volumes of a least 1 mL for inhalation therapy using nebulizers. Assuming at least 1 mL of volume for delivery, a POSA as of 2006 would thus reasonably understand that Voswinkel JESC delivered at least **16, 32, 48, or 64 µg** (16, 32, 48, 64 µg/mL*1 mL) of inhaled treprostinil to patients.

- "[A]t least" 1 mL has no upper bound: unhelpful to calculate actual delivered dose
- Dr. Hill conflates fill volume and delivered volume

Sources: Paper No. 18, 28; Paper No. 29, 25-26; EX1002, ¶65; EX2055 (Hill Dep.), 146:16-23.

Calculation #1: POSA's General Knowledge Cannot Supply Missing Limitation



1330 948 FEDERAL REPORTER, 3d SERIES

Brown v. City of Fort Lauderdale, 923 F.2d 1474, 1481 (11th Cir. 1991) (emphasis added). In other words, Johnson does not need to prove that Gimenez had *actual* knowledge of constitutional violations to prevail—Johnson must prove only that there were enough violations over a substantial enough period of time to show that Gimenez *must have known* about the violations and, yet, failed to stop them. This information is accessible from sources other than Gimenez. Therefore, Gimenez's deposition testimony is unnecessary, and the District Court did not abuse its discretion in denying Johnson the opportunity to depose him.

VI.

Accordingly, the District Court's judgment is

AFFIRMED in part, VACATED in part, and REMANDED for reconsideration.

TJOFLAT, Circuit Judge, specially concurring:

I concur fully in the judgment of the Court. I write separately because I disagree that parallel Title VII and § 1983 claims should be decided based on identical methods of proof, such as the *McDonnell Douglas* framework.

To establish a 42 U.S.C. § 1983 claim against a municipality, "a plaintiff must show: (1) that his *constitutional* rights were violated; (2) that the municipality had a custom or policy that constituted deliberate indifference to that *constitutional* right; and (3) that the policy or custom caused the violation." *McDowell v. Brown*, 392 F.3d 1283, 1289 (11th Cir. 2004) (emphases added). However, in this Circuit, when § 1983 and Title VII are used as parallel causes of action to remedy the same underlying discriminatory conduct, both claims are analyzed under the *McDonnell Douglas* framework for the purposes of summary judgment. In my view, it is improper to use *McDonnell Douglas*'s burden-shifting framework, which utilizes presumptions based on the *statutory* Title VII scheme, to analyze § 1983 claims which are necessarily *constitutional* in nature—even where the § 1983 claim is based on the same misconduct as the Title VII claim. In other words, *McDonnell Douglas* is properly used only to vindicate the rights protected by the Title VII statutory scheme. It should not be used outside of that narrow context. To the extent that cases in our Circuit suggest otherwise, I believe the issue should be reconsidered by this Court *en banc*.

KEY NUMBER SYSTEM

KONINKLIJKE PHILIPS N.V., Appellant

v.

GOOGLE LLC, Microsoft Corporation, Microsoft Mobile Inc., Appellees

2019-1177

United States Court of Appeals, Federal Circuit.

Decided: January 30, 2020

Background: Challenger filed petition for inter partes review of patent related to a method of forming a media presentation using a control information file that offered media presentation in multiple alternative formats and provided media presentation in multiple files. The United States Patent and Trademark Office, Patent Trial and Appeal Board (PTAB), Weinschenk, Administrative Patent Judge, 2018 WL

this case violates *Arendi*. In *Arendi*, we cautioned that although "common sense and common knowledge have their proper place in the obviousness inquiry," (a) invoking "common sense . . . to supply a limitation that was admittedly *missing* from the prior art" should generally only be done when "the [missing] limitation in question [is] unusually simple and the technology particularly straightforward;" and (b) references to common sense "cannot be used as a wholesale substitute for reasoned analysis and evidentiary support." 832 F.3d at 1361–62. We concluded

Source: *Koninklijke Philips N.V. v. Google LLC*, 948 F.3d 1330 (Fed. Cir. 2020) (cited in Paper 18 (ID), 24-25).

Calculation #1: Liquidia's Three Volume Exhibits Are Not Probative

- Do not address treprostinil
  - *EX1066:* AccuNeb label (albuterol sulfate - relieve bronchospasm)
  - *EX1029:* Ventavis label (iloprost – pulmonary hypertension)
  - *EX1050:* Pulmozyme label (rhDNase – improve pulmonary function for cystic fibrosis patients)

Sources: Paper No. 18, 24; EX1029, 1; EX1050, 1; EX1066, 1; EX2001, ¶41.

Calculation #1: Liquidia's "Delivered" Is Not Delivered

Liquidia says:	In fact, then FDA-approved dosing included teachings of *delivering* at least 1mL of solution. (*See, e.g.*, EX1050, 2 (Pulmozyme label teaches dosing of a "single-use ampule inhaled once daily" where each ampule "*delivers* 2.5mL of ... solution") (emphasis added).)
Label actually says:	Pulmozyme is administered by inhalation of an aerosol mist produced by a compressed air driven nebulizer system (see Clinical Experience, DOSAGE AND ADMINISTRATION). Each Pulmozyme single-use ampule will deliver 2.5 mL of the solution to the nebulizer bowl. The aqueous solution contains 1.0 mg/mL dornase alfa, 0.15 mg/mL calcium chloride dihydrate and 8.77 mg/mL sodium chloride. The solution contains no preservative. The nominal pH of the solution is 6.3.

Sources: Paper No. 44, 11-12; Paper No. 55, 13; EX1004, 33 n.4; EX1050; *see also* EX2056, 127:25-128:4.

Calculation #1: Liquidia's Three Exhibits Talk About The Wrong Volume

- EX1029, EX1050, EX1066 at most disclose fill volume
- Delivered volume depends on nebulized volume, which depends on fill **and residual** volume
- Liquidia's EX1037 (OptiNeb Manual) states that residual volume may vary from 0.5 ml – 1.5 ml
  (EX1037, 22; *see also* EX2076 (citing residual volumes 0.5-2.3 mL))

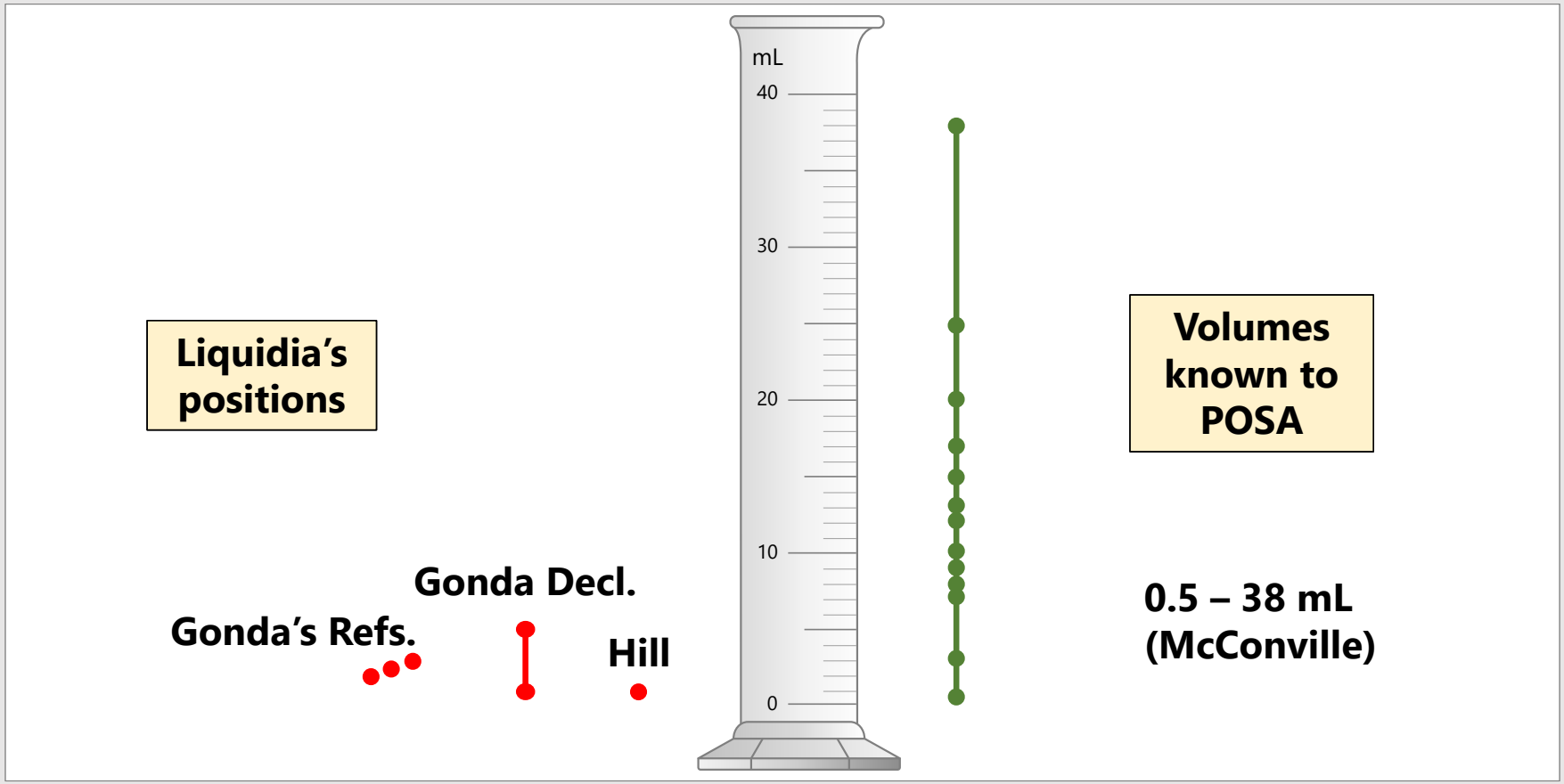
NOTE
The remaining quantity left in the medication cup depends on the selected program:

P1	– approx. 0.5–1.5 ml remaining quantity
P2	– approx. 0.5–1.5 ml remaining quantity
P3/P4/P5/P6	– approx. 0.5 ml remaining quantity

Sources: Paper No. 55, 12-13; EX1029; EX1050; EX1066; EX1037; EX2076.

Calculation #1: Fill Volumes, If Relevant, Vary Widely

No basis to assume any given volume was used in JESC



Sources: Paper No. 55, 11-13; EX1004, ¶56, ¶56, n.4; EX2053, ¶71.

Calculation #1: Additional Volume Unknowns and Flaws

UNKNOWNS

- Fill volume in JESC
- Residual volume
- Whatever the fill volume, whether it was used for one or multiple administrations
- Which nebulizer was used
- Patient factors – size, breathing pattern, breath depth
- Volume actually delivered

FLAWS

- Gonda did not survey all available nebulizers to assess alleged "typical" fill or delivered volumes
- Unsupported assumption that JESC used treprostinil from ampules
- Failure to account for device losses (inefficiency)

Sources: Paper No. 29, 21-22, 28, 30-32, 44; Paper No. 55, 11-13; EX2053, 30, 32, 36-37; EX2097, 160:12-17.

1 Volume Flaws

2 Rate Flaws

3 Efficiency Flaws

Calculation #1: Many Factors Affect Actual Output Rates

A review of the technical aspects of drug nebulization

P. Le Brun, Harry Heijerman

Pharmacy world & science : PWS

IPR2021-00406
United Therapeutics EX2075

In practice, there exists a wide variation in the performance of different types of nebulizers [9 19 20]. Droplet size distribution and output rate are also influenced by the physical properties of the drug solution (suspension) and air flow rate from the compressor. These variables make a careful selection critical for an optimal therapy with this type of inhalation system.

In an ultrasonic nebulizer, droplets are produced by a rapidly vibrating piezoelectric crystal. The frequency of the vibrating crystal determines the droplet size for a given solution. In most ultrasonic nebulizers the

Drug output and drug output rate

As explained above for the several types of jet nebulizers, the output rate of the breath assisted, open vent type is larger than the output rate of the open vent nebulizer, which consequently has a higher output rate when compared to the conventional nebulizer [20 36 37 38]. Above mentioned factors for the droplet size distribution are also applicable to the drug output rate. Gas flow in jet nebulizers and vibration frequency in ultrasonic are proportionally related to drug output rate [25 39].

Furthermore, the breathing pattern through the nebulizer influences the actual inhaled dose. It influ-

Sources: EX2075, 77, 79, 80; *see also* EX2053, ¶¶52, 55.

Calculation #1: Nebulizer Output Rates Vary By Brand Even For Same Drug

Medication Nebulizer Performance*

Effects Of Diluent Volume, Nebulizer Flow, and Nebulizer Brand

Dean Hess, PhD, RRT; Daniel Fisher, BS, RRT; Parris Williams, BS, RRT; Sharon Pooler, RRT; and Robert M. Kacmarek, PhD, RRT

Background: **Medication nebulizers are commonly used to delivery aerosolized medications to patients with respiratory disease. We evaluated output and respirable aerosol available to the patient (inhaled mass) for 17 medication nebulizers using a spontaneous breathing lung model.**
Methods: **Three nebulizer fill volumes (3, 4, and 5 mL containing 2.5 mg of albuterol) and 3 oxygen flows (6, 8, and 10 L/min) were evaluated using the 17 nebulizers. A cotton plug at the nebulizer mouthpiece was used to trap aerosol during simulated spontaneous breathing. Following each trial, the amount of albuterol remaining in the nebulizer and the amount deposited in the cotton plug were determined spectrophotometrically. Aerosol particle size was determined using an 11-stage cascade impactor.**
Results: **Increasing fill volume decreased the amount of albuterol trapped in the dead volume ($p<0.001$) and increased the amount delivered to the patient ($p<0.001$). Increasing flow increased the mass output of particles in the respirable range of 1 to 5 μm ($p=0.004$), but the respirable mass delivered to the patient was affected to a greater extent by nebulizer brand ($p<0.001$) than flow. Although 2.5 mg of albuterol was placed into the nebulizers, less than 0.5 mg in the respirable range of 1 to 5 μm was delivered to the mouthpiece.**
Conclusions: **The performance of medication nebulizers is affected by fill volume, flow, and nebulizer brand. When they are used for research applications, the nebulizer characteristics must be evaluated and reported for the conditions used in the investigation.** ***(CHEST 1996; 110:498-505)***

Key words: aerosol therapy; inhaled bronchodilator administration; nebulizers

Abbreviations: GSD=geometric standard deviation, MMAD=mass median aerodynamic diameter

Despite the common use of metered-dose inhalers and the availability of dry powder inhalers, aerosolized medications are still frequently administered by nebulizer. Nebulizers are commonly used for inhaled bronchodilator administration to patients with reactive airways, including the perioperative and postoperative treatment of these patients. Advantages of nebulizers include the ability to use them with patients who cannot coordinate the use of a metered-dose inhaler[1] and the ability to conveniently administer a large (or continuous) dose into the lungs.[2] Important characteristics of nebulizer performance include the drug output, the aerosol particle size generated, the nebulization time, and the amount of drug delivered to the patient. Factors that have been shown to affect nebulizer performance include device construction (ie, manufacturer), fill volume, flow, temperature, and humidity of the driving gas.[1]

For editorial comment see page 316

A common feature of nebulizers is dead volume, which is the volume of solution that remains in the nebulizer cup after aerosol production ends. Previous studies have typically evaluated dead volume by serial weighing.[3-5] This method does not adequately characterize drug output and amount of drug in the dead volume due to reconcentration in the nebulizer cup.[6,7] Reconcentration occurs because of evaporation owning to the low relative humidity of the gas powering the nebulizer. Nebulizer output should be determined more appropriately by measuring the amount of medication that remains after aerosol production is complete.

Particle size is an important characteristic of nebulizer performance. Particles too large do not reach the

*From the Department of Respiratory Care, Massachusetts General Hospital, and Harvard Medical School, Boston.
Presented, in part, at the annual meeting of the American Association for Respiratory Care, Las Vegas, December 1994.
Supported, in part, by Puritan-Bennett, Hudson RCI, Marquest, Professional Medical, SIMS.
Manuscript received October 20, 1995; revision accepted February 26, 1996.
Reprint requests: Dr. Hess, Respiratory Care, Ellison 401, Massachusetts General Hospital, Boston, MA 02114

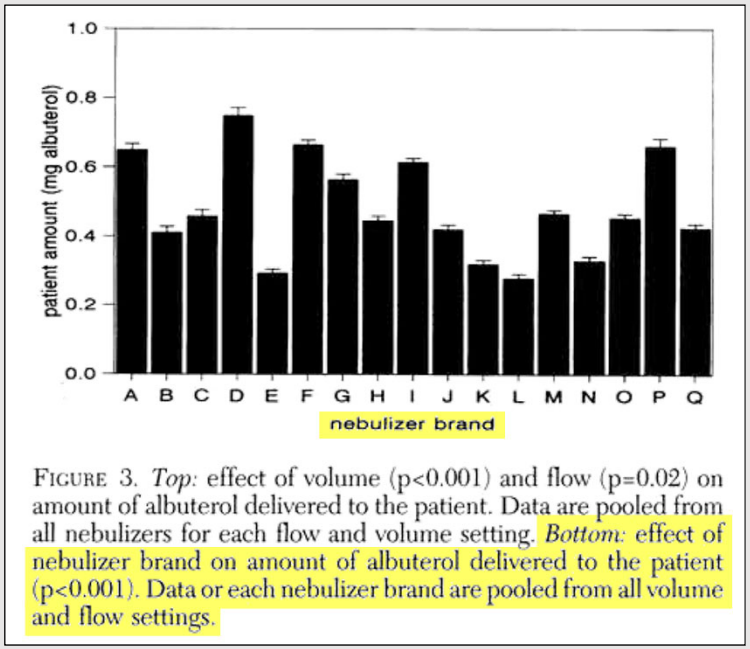
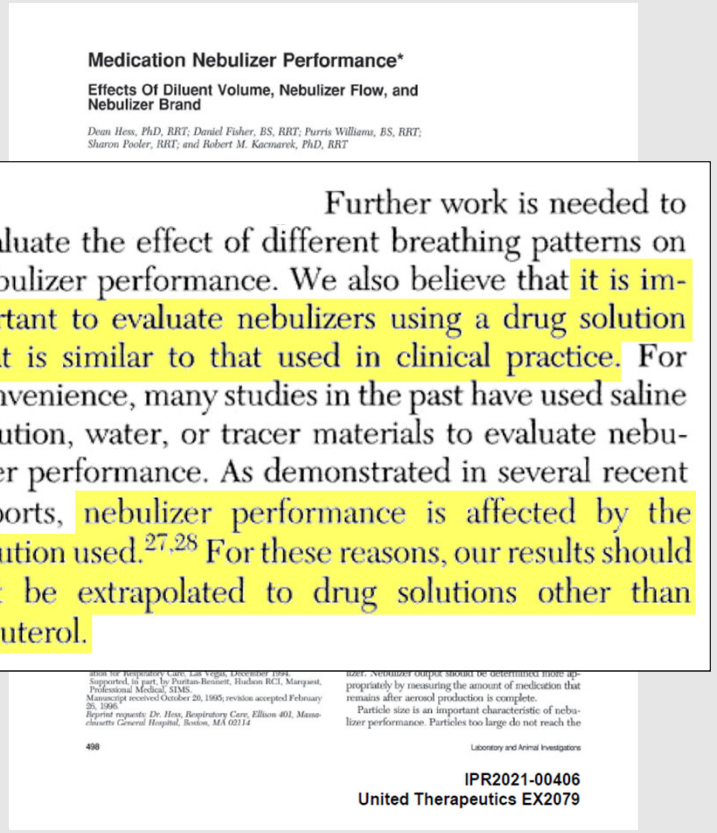


FIGURE 3. *Top:* effect of volume ($p<0.001$) and flow ($p=0.02$) on amount of albuterol delivered to the patient. Data are pooled from all nebulizers for each flow and volume setting. *Bottom:* effect of nebulizer brand on amount of albuterol delivered to the patient ($p<0.001$). Data or each nebulizer brand are pooled from all volume and flow settings.

Sources: Paper No. 55, 13-16; EX2053, ¶¶ 52, 55-56, 58; EX2079, 4.

Calculation #1: Drug Solution Affects Delivered Dose



Medication Nebulizer Performance*

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Dean Hess, PhD, RRT; Daniel Fisher, BS, RRT; Purris Williams, BS, RRT; Sharon Pooler, RRT; and Robert M. Kacmarek, PhD, RRT

Further work is needed to evaluate the effect of different breathing patterns on nebulizer performance. We also believe that it is important to evaluate nebulizers using a drug solution that is similar to that used in clinical practice. For convenience, many studies in the past have used saline solution, water, or tracer materials to evaluate nebulizer performance. As demonstrated in several recent reports, nebulizer performance is affected by the solution used.[27,28] For these reasons, our results should not be extrapolated to drug solutions other than albuterol.

Supported, in part, by Puritan-Bennett, Hudson RCI, Marquest, Professional Medical, SIMS.
Manuscript received October 20, 1995; revision accepted February 20, 1996.
Reprint requests: Dr. Hess, Respiratory Care, Ellison 401, Massachusetts General Hospital, Boston, MA 02114

propriately by measuring the amount of medication that remains after aerosol production is complete.

Particle size is an important characteristic of nebulizer performance. Particles too large do not reach the

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Sources: EX1066; EX2053, ¶¶ 60-61; EX2079, 7-8.

Calculation #1: POSA Would Not Know Output Rate In JESC

McConville:

Voswinckel JESC provides no delivered dose information, however, and, in fact, provides:

- No details on the formulation, such as:
  - What the treprostinil was dissolved in (note that Vos JESC describes the placebo as a "solvent solution," without disclosing the solvent)
  - Whether the formulation comprised any excipients, and if so, which How the solution was prepared
- No details about the "OptiNeb" nebulizer itself, other that it was an ultrasound nebulizer

- No details on patient factors[10]
  - No details on the number of breaths taken
  - No details on breathing rate
  - No details on breathing depth (shallow, deep, normal)
  - Whether the patient exhaled through the device or removed the mouthpiece, mask, or other interface to exhale
- No testing data on dose actually delivered to the patient

- No details about how the nebulizer was used, other than solution concentration:[7]
  - No details on how much treprostinil solution was put into the nebulizer reservoir
  - No details on how much treprostinil solution remained in the reservoir after 6 minutes[8]
  - No details on which frequency the nebulizer's ultrasound generator operated
  - No details on the MMAD aerosol size generated (i.e. what nebulizer baffle size may have been used)
  - No details related to aerosol output rate (e.g. continuous, pulse, etc.)
  - No details on the interface between the nebulizer and patient (e.g., mouthpiece, face mask, etc.)
  - No details on the pathway the aerosol travels to the patient, such as the nebulizer interior geometry or tubing connected to the nebulizer
  - No details on whether the nebulizer was tapped to dislodge particles or droplets adhering inside the nebulizer[9]

Source: EX2053, ¶55.

Calculation #1: Liquidia's Rate Calculations Are Flawed

- Liquidia asserts that volume can be calculated from rates
  - e.g., 0.6 mL/min x 6 min = volume
- Liquidia's overly simplistic math fails:
  - No basis to rely on 0.6 mL/min rate for treprostinil at the mouthpiece (from EX1037 or otherwise)
  - Rates are affected by numerous factors
- Liquidia's unsupported rate reduction
  - Hill asserts 0.5 and 0.6 in Reply, without basis
- POSA would not infer a dose from unreliable rates

Sources: Paper No. 2, 23-24; Paper No. 29, 26, 28-29; EX1002, ¶¶ 67, 99-100; EX1006, ¶¶ 61, 909-100.

Calculation #1: Dr. Hill Had No Basis For Asserted 0.5 ml/min Rate

Hill Reply Decl.

determine the single event dose administered in Voswinckel JESC. In my clinical experience, the average nebulization rate for continuous nebulizers in the 2006 timeframe was 0.5 to 0.6 mL/min. *E.g.*, Ex. 1037 at 28 (disclosing a nebulizing rate of 0.6 mL/min). A POSA would not have needed to determine a precise dosage

Hill Deposition (Apr. 13, 2022)

Q. So in paragraph – excuse me, paragraph 61, the evidence you cite for the 0.6 rate is the exhibit 1037 English translation OptiNeb user manual 2005?

A. Yes, and including my clinical experience.

Q. And you don't cite there in paragraph 61 a separate document that specifically discloses a nebulizing rate of 0.5 milliliters per minute?

A. I don't believe so, no.

Sources: Paper No. 64, 1; EX1106, ¶¶ 61, 90; EX2108 23:1-11.

Calculation #1: Petition Cites EX1037 And Relies On 0.6 mL/min Rate

Petition for *Inter Partes Review* of
U.S. Patent No. 10,716,793 B2

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

IPR2021-00406
U.S. Patent No. 10,716,793 B2
Issue Date: July 21, 2020

Title: Treprostinil Administration by Inhalation

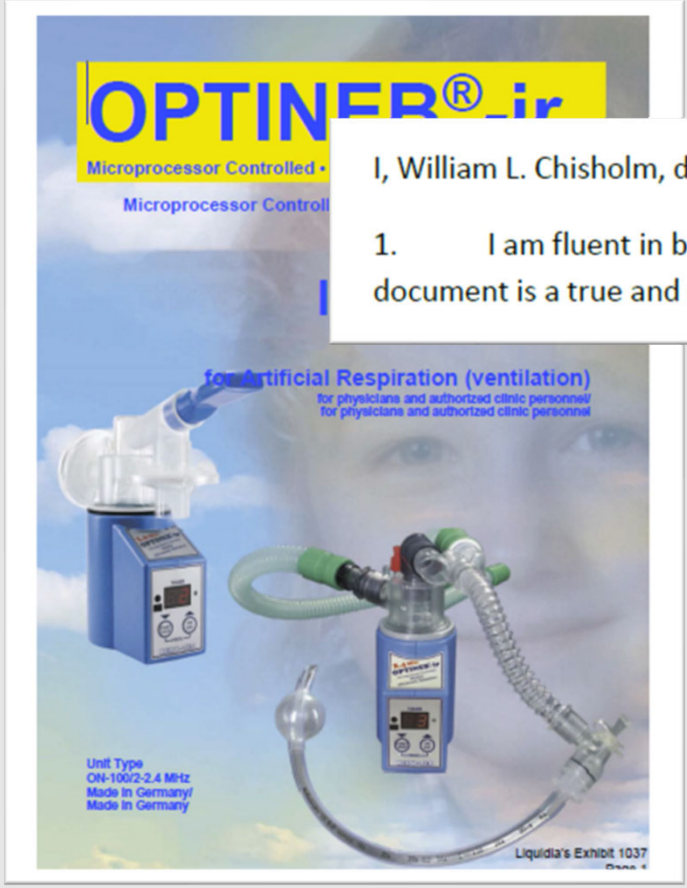
PETITION FOR *INTER PARTES* REVIEW OF U.S. Patent No. 10,716,793 B2

- English only

In fact, a POSA would have expected the OptiNeb® device used at the time (before 2006) to nebulize (i.e., turned liquid to aerosol) at a rate of 0.6 mL of solution per minute. EX1002, ¶67 (citing EX1037, 28.)

Sources: Ex1037; Paper No. 2, 23; EX1002, ¶67; Paper No. 29, 26-27.

Calculation #1: EX1037 Threshold Issues



I, William L. Chisholm, declare that:

1. I am fluent in both German and English. To the best of my knowledge and belief, the attached document is a true and correct translation of a user manual for OPTINEB®-ir from German to English.

- No copy of document that was allegedly translated
- No basis for public accessibility before priority date

Sources: Paper No. 29, 27; Paper No. 55, 11-12, n.5; Paper No. 66, 4-5; EX1037.

Calculation #1: EX1037 Is Not Substantively Helpful

- Hill and Gonda's 0.6 mL/min rate
  - Measured or just a target?
  - What solution?
  - Continuous/intermittent?
  - Real life: would not output 0.6 mL/min
- Unknowns Gonda admits affect output
  - Frequency
  - Baffle plates
  - Connection to patient
  - Program used

Sources: Paper No. 29, 28-29; Paper No. 55, 13-15; EX2053, ¶52; EX2056, 81:17-89:18, 93:16-25.

Calculation #1: JESC Does Not Identify Which OptiNeb Model Was Used

Volume 25 Abstract Supplement August/September 2004 ISSN 0195-668X

EUROPEAN SOCIETY OF CARDIOLOGY

European Heart Journal

Journal of the European Society of Cardiology

Methods: Open-label, single blind placebo-controlled clinical study. After placement of a Swan-Ganz catheter and a femoral artery line, patients inhaled solvent solution (placebo) (n=8) or treprostinil for 6 min (OptiNeb ultrasound nebulizer, Nebu-tec, Germany) in concentrations of 16, 32, 48, and 64 µg/ml (n=6, 6, 6, and 3 patients). Measurement was performed before and after 0, 15, 30, 60, 90, 120, 150 and 180 min. The mean area between the placebo and the treprostinil curves (ABC186) was calculated (baseline=100%).

Liquidia's Exhibit 1007
Page 1

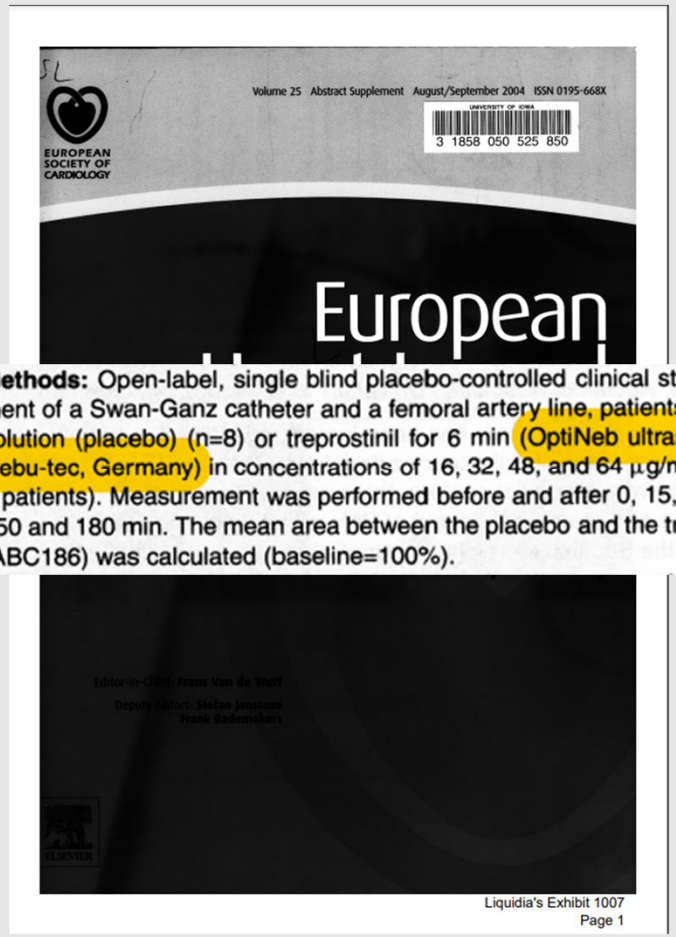
14 Q. Do you know if all OptiNebs are IR
15 OptiNebs?
16 A. No, but I see the term "OptiNeb Pro" used
17 with some of them, so I don't think so, but I don't
18 know for a fact.
19 Q. So there are some OptiNebs that have a
20 moniker, "pro" after them, and you don't know
21 whether those are the same or different than the
22 OptiNeb-IR?
23 A. Correct.

16 Do you know if this is an OptiNeb-IR?
17 A. I don't know.
18 Q. Do you know if this is OptiNeb-Pro?
19 A. I don't know that.
20 Q. Do you know if this is an OptiNeb model
21 ON-100-2 [sic]?
22 A. It doesn't say that here.

7 Q. Do you know if there are any other
8 OptiNeb-IRs that have model numbers other than
9 ON-100/2?
10 A. I don't know that.

Sources: EX1007, 7; EX2055, 61:14-23, 81:16-22, 93:7-10.

Calculation #1: JESC Does Not Identify Which Frequency Was Used



Volume 25 Abstract Supplement August/September 2004 ISSN 0195-668X

3 1858 050 525 850

EUROPEAN SOCIETY OF CARDIOLOGY

European

Methods: Open-label, single blind placebo-controlled clinical study. After placement of a Swan-Ganz catheter and a femoral artery line, patients inhaled solvent solution (placebo) (n=8) or treprostinil for 6 min (OptiNeb ultrasound nebulizer, Nebu-tec, Germany) in concentrations of 16, 32, 48, and 64 µg/ml (n=6, 6, 6, and 3 patients). Measurement was performed before and after 0, 15, 30, 60, 90, 120, 150 and 180 min. The mean area between the placebo and the treprostinil curves (ABC186) was calculated (baseline=100%).

Liquidia's Exhibit 1007
Page 1

12	Q. Do you know what those frequencies would refer
13	to?
14	A. They would be the frequency of the ultrasound
15	that's closing the waves that break up the liquid that
16	causes the nebulization.
17	Q. And would those frequencies have an effect on
18	performance of the device?
19	A. It's possible.
20	Q. And is that another area where to really do
21	the comparison you would want to go to the laboratory
22	and measure the output of each to be able to compare the
23	performance of 1.6 megahertz versus 2.4?
24	A. Yes, I would.

Sources: EX1007, 7; EX2056, 83:12-24.

Calculation #1: JESC Does Not Identify Which Program Was Used

8.2.1 Features of the first program (P1)
Program 1 was developed for the nebulization of special medications.
Non-adjustable nebulization time: max. 12 minutes. Time indication on the display runs from "0" going forward until the pre-set time is reached. The aerosol is intermittently generated (no continuous aerosol production). After expiry of the pre-set time, the program is ended.

8.2.2 Features of the second program (P2)
Program 2 was developed for the nebulization of special medications.
Non-adjustable nebulization time: max. 12 minutes.
Time indication on the display runs from "0" going forward until the pre-set time is reached. The aerosol is intermittently generated (no continuous aerosol production). After expiry of the pre-set time, the program is ended. The user is not able to change the program parameters.

8.2.3 Features of the third program (P3)
No fixed nebulization time. The device is volume-controlled (remaining quantity recognition) and produces aerosol until the medication has been nebulized. The **OPTINEB®-ir** ultrasonic nebulizer switches off automatically after reaching a remaining quantity of approx. 0.5 ml. The inhalation time may differ in length and results from the set ventilation parameters, the respiratory rate and the depth of respiration

8.2.4 Features of the fourth program (P4)
Corresponds to Program P3 but without the initial intermittent time period. The user is not able to change the program parameters.

8.2.5 Features of the fifth program (P5)
Program P5 corresponds to the **OPTINEB** in the conventional version with the following features:
- Flexibly adjustable inhalation time. Preference settings 1 to 15 minutes.
- After expiry of the set time, the program is ended.
- The user can re-program the inhalation time within the pre-set range (see instruction manual for patients).

8.2.6 Features of the sixth program (P6)
The program was designed for ventilation purposes. The active output intervals and the pause times are adjustable using the keypad. (See Point 8.3 Individual programming of Program 6 with the **OPTINEB®-ir**)

- EX1037: 6 different programs
- Different programs can give different outputs
  - McConville: "Especially because the programs affect whether the nebulizer would run continuously or intermittently, and for how long, the POSA would understand that the programs would affect nebulizer output."
- JESC does not describe which program was used

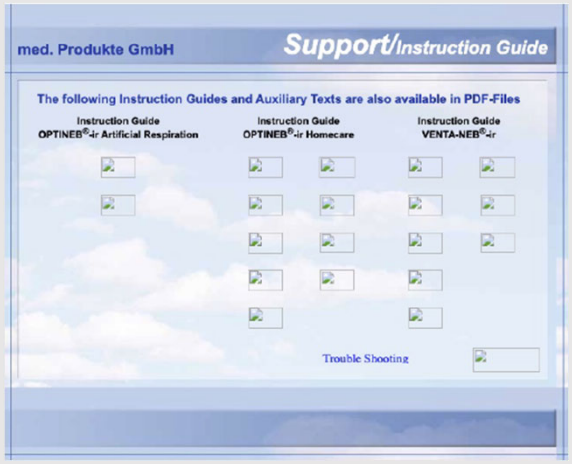
Sources: Paper No. 29, 28-29; EX1007, 7; EX1037, 18-20; EX2053, ¶79, *see also* ¶78.

Calculation #1: Liquidia's Reliance On 0.6 mL/min Is Misplaced

Document	English	German	Rate
EX1037		?	0.6 mL/min
EX1086			<0.6 mL/min
EX1087	?		<0.6 mL/min

Sources: EX1037, 28; EX1086 (provided as exhibit to EX2108), 31, 50; EX1087, 27.

Calculation #1: EX1087 and EX1086 Do Not Fix EX1037's Problems



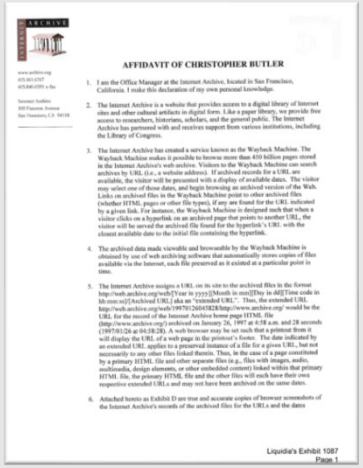
- Even if EX1037 is not excluded, Petitioner has not shown it to be publicly available
- EX1087 does not prove availability
  - No evidence that web pages for Optineb manual existed on the same date as the manual
- EX1087, Ex. D
  - Multiple potential links to manuals
  - No evidence identifying which the POSA would allegedly use
  - Unclear which, if any, leads to EX1087, Ex. E

Sources: Paper No. 29, 26-27; EX1087; Paper No. 72, 1-2, 5.

Calculation #1: EX1087 Shows Less Than 0.6 mL/min Rate

EX1087:

Butler Decl.



AFFIDAVIT OF CHRISTOPHER BUTLER

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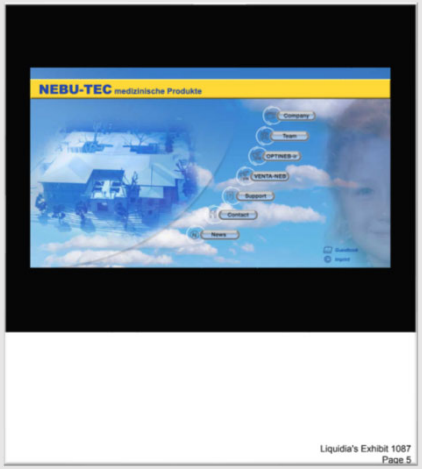
3. The Internet Archive has created a service known as the Wayback Machine. The Wayback Machine makes it possible to browse more than 410 billion pages stored in the Internet Archive's web archive. Visitors to the Wayback Machine can search archives by URL (i.e., a website address). If archived records for a URL are available, the visitor will be presented with a display of available dates. The visitor may select one of those dates, and begin browsing an archived version of the Web. Links on archived files in the Wayback Machine point to other archived files (whether HTML pages or other file types), if any are found for the URL indicated by a given link. For instance, the Wayback Machine is designed such that when a visitor clicks on a hyperlink on an archived page that points to another URL, the visitor will be served the archived file found for the hyperlink's URL with the closest available date to the initial file containing the hyperlink.
4. The archived data made viewable and browsable by the Wayback Machine is obtained by use of web archiving software that automatically stores copies of files available via the Internet, each file preserved as it existed at a particular point in time.
5. The Internet Archive assigns a URL on its site to the archived files in the format http://web.archive.org/web/[Year in yyyy][Month in mm][Day in dd][Time code in hh:mm:ss]/[Archived URL] (aka an "extended URL"). Thus, the extended URL http://web.archive.org/web/19970126045828/http://www.archive.org/ would be the URL for the record of the Internet Archive home page HTML file (http://www.archive.org/) archived on January 26, 1997 at 4:58 a.m. and 28 seconds (19970126 at 04:58:28). A web browser may be set such that a printout from it will display the URL of a web page in the printout's footer. The date indicated by an extended URL applies to a preserved instance of a file for a given URL, but not necessarily to any other files linked therein. Thus, in the case of a page constituted by a primary HTML file and other separate files (e.g., files with images, audio, multimedia, design elements, or other embedded content) linked within that primary HTML file, the primary HTML file and the other files will each have their own respective extended URLs and may not have been archived on the same dates.
6. Attached hereto as Exhibit D are true and accurate copies of browser screenshots of the Internet Archive's records of the archived files for the URLs and the dates

Liquidia's Exhibit 1087
Page 1

Ex. D – URLs, screenshots



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Page 5

Ex. E – OptiNeb-ir manual - German

Liquidia's Exhibit 1087
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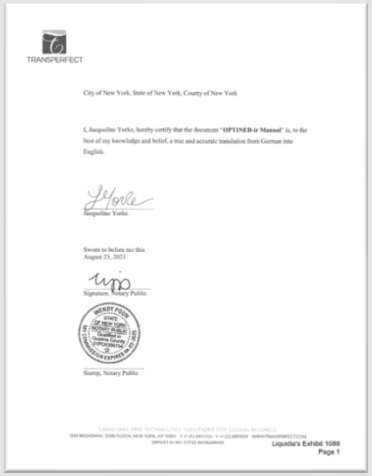
Ex. F - HTML

Liquidia's Exhibit 1087
Page 30

Verneblerleistung	< 0,6 ml/min

Source: EX1087, 27.

Calculation #1: EX1086 Describes Less Than 0.6 mL/min Rate



TRANSPERFECT

City of New York, State of New York, County of New York

I, Jacqueline Yorke, hereby certify that the document "OPTINEB-ir Manual" is, to the best of my knowledge and belief, a true and accurate translation from German into English.

Jacqueline Yorke

Sworn to before me this August 23, 2021

Signature, Notary Public

Stamp, Notary Public

Liquidia's Exhibit 1086
Page 1

ENGLISH TRANSLATION

OPTINEB®-ir

Microprocessor Controlled • Mobile Ultra-sonic Nebulizer

Mikroprozessor gesteuerter mobiler Ultraschallvernebler

Gebrauchsanweisung

Operating Instructions

für Beatmung / for Artificial Ventilation

für Ärzte und autorisiertes Klinikpersonal/
for physicians and authorized clinic personnel

Gerätetyp / Unit Type
ON-100/2-2,4 MHz
Hergestellt in Deutschland/
Made in Germany

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Page 4

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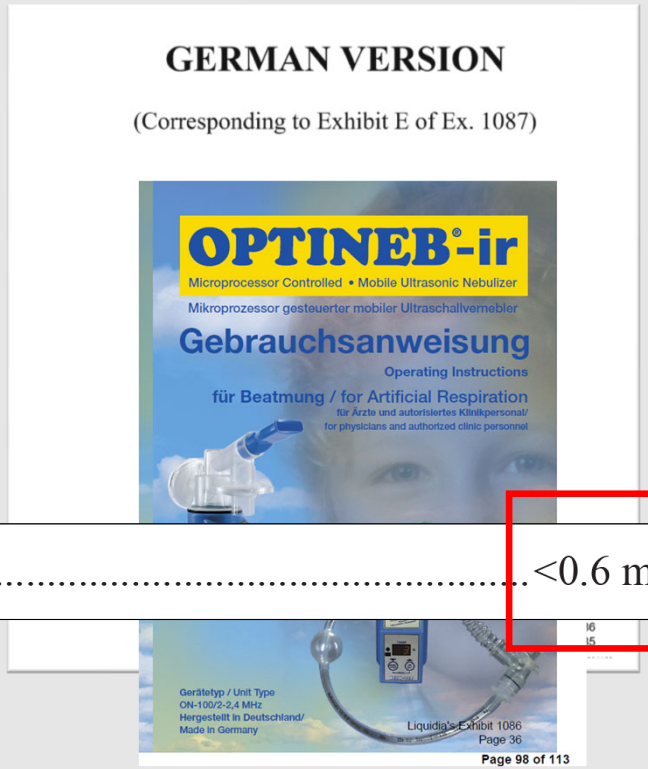

GERMAN VERSION

(Corresponding to Exhibit E of Ex. 1087)

OPTINEB®-ir

Microprocessor Controlled • Mobile Ultrasonic Nebulizer

Mikroprozessor gesteuerter mobiler Ultraschallvernebler

Gebrauchsanweisung

Operating Instructions

für Beatmung / for Artificial Respiration

für Ärzte und autorisiertes Klinikpersonal/
for physicians and authorized clinic personnel

Gerätetyp / Unit Type
ON-100/2-2,4 MHz
Hergestellt in Deutschland/
Made in Germany

Liquidia's Exhibit 1086
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Nebulizer output.....<0.6 ml/min

Source: EX1086, 31 (English), 50 (German).

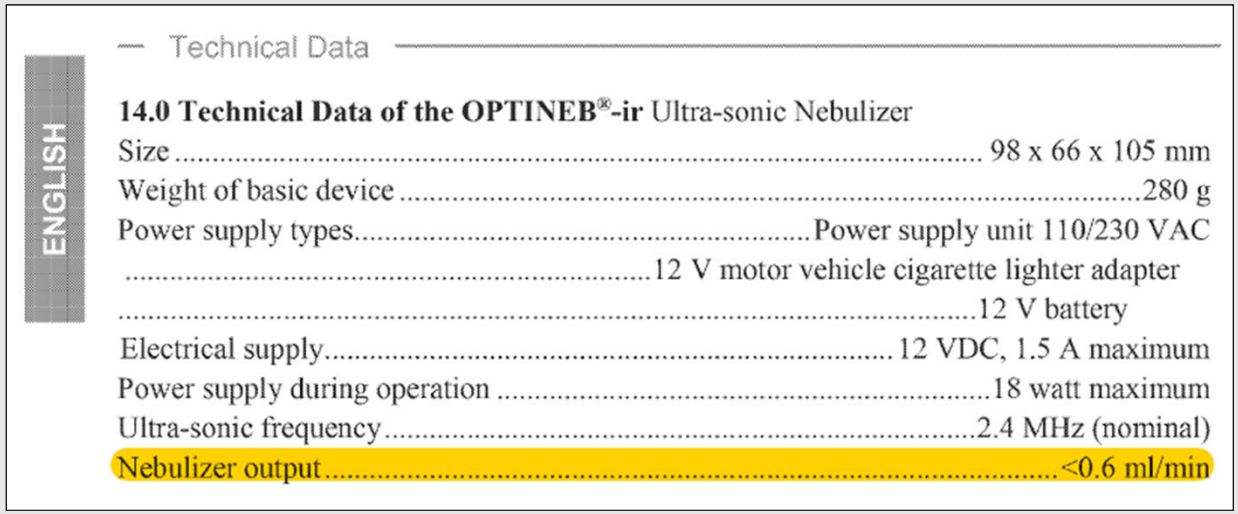
Calculation #1: EX1087 Does Not Fix EX1037 Issues

- Liquidia asserted EX1037 was from 2005
- Liquidia's declarant in EX1087 states the manual is from 2004
- Rates in EX1037 and EX1087 **don't match**
- <0.6 mL/min teaches away from Liquidia's JESC calculation

EX1037	EX1087 (German)	EX1086 (English)
14.0 Technical data of the OPTINEB®-ir ultrasonic nebulizer Size ..... 98 x 66 x 105 mm Weight of basic device .....280 g Power supply type ..... Power supply unit 110/230 VAC ..... 12 V motor vehicle cigarette lighter adapter ..... 12 V battery Electrical supply ..... 12 VDC, 1.5 A maximum Power consumption during operation .....18 watt maximum Ultrasonic frequency ..... 2.4 MHz (nominal) Nebuliser output ..... 0.6 ml/min MMAD ..... 2.3/3.3/3.8/4.5 µm (depending on baffle plate) Capacity of the medication cup ..... 7.5 ml maximum Capacity of the contact fluid reservoir .....45 ml Electrical protection class ..... II type B	**14.0 Technische Daten des Ultraschallverneblers OPTINEB®-ir** Größe .....98 x 66 x 105 mm Gewicht des Grundgerätes.....280 g Stromversorgungsarten.....Netzgerät 110/230 VAC .....12 V Kfz-Adapter Zigarettenanzünder .....12 V Akku Elektrische Versorgung.....12 VDC, 1,5 A Maximum Stromverbrauch bei Betrieb.....18 Watt Maximum Ultraschallfrequenz .....2,4 MHz(nominal) Verneblerleistung .....< 0,6 ml/min MMAD.....2,3/3,3/3,8/4,5 µm (je nach Prallplatte) Fassungsvermögen des Medikamentenbechers .....7,5 ml Maximum Fassungsvermögen des Kontaktflüssigkeitsbehälters.....45 ml Elektrische Schutzklasse .....II Typ B	.... 98 x 66 x 105 mm .....280 g ly unit 110/230 VAC ette lighter adapter ...12 V battery DC, 1.5 A maximum .....18 watt maximum ...2.4 MHz (nominal) .....<0.6 ml/min nding on baffle plate) ..... 7.5 ml maximum .....45 ml ..... II type B

Sources: Paper No. 55, 11-12; Paper No. 64, ¶4; EX1037, 28; EX1086, 31; EX1087, 27.

Calculation #1: EX1086 Shows OptiNeb Rate Is Not 0.6 mL/min



ENGLISH

Technical Data

14.0 Technical Data of the OPTINEB®-ir Ultra-sonic Nebulizer

Size	98 x 66 x 105 mm
Weight of basic device	280 g
Power supply types	Power supply unit 110/230 VAC
	12 V motor vehicle cigarette lighter adapter
	12 V battery
Electrical supply	12 VDC, 1.5 A maximum
Power supply during operation	18 watt maximum
Ultra-sonic frequency	2.4 MHz (nominal)
Nebulizer output	<0.6 ml/min

Q. Exhibit 1086 does not describe the nebulizer output as 0.6 milliliters per minute. It actually describes it as less than 0.6; correct?

A. That's what it says, yes.

Q. And then just numerically, 0.5 milliliters per minute as a rate is less than .6; correct?

A. Yes, it is.

Q. 0.3 milliliters per minute is also less than 0.6; correct?

A. Yes, it is.

Q. 0.1 milliliters per minute is also less than 0.6; correct?

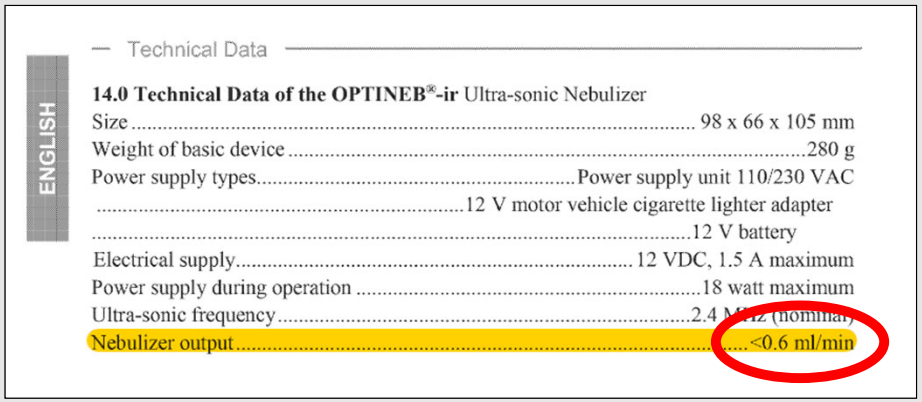
A. Yes.

Sources: Paper No. 64, ¶4; EX1086; EX1087; EX2108, 29:3-16.

Calculation #1: Liquidia Failed To Point Out "<0.6 ml/min"

On September 8, 2021:

- Liquidia provided EX1086, EX1087



Technical Data

ENGLISH

14.0 Technical Data of the OPTINEB®-ir Ultra-sonic Nebulizer

Size	98 x 66 x 105 mm
Weight of basic device	280 g
Power supply types	Power supply unit 110/230 VAC
	12 V motor vehicle cigarette lighter adapter
	12 V battery
Electrical supply	12 VDC, 1.5 A maximum
Power supply during operation	18 watt maximum
Ultra-sonic frequency	2.4 MHz (nominal)
Nebulizer output	<0.6 ml/min

On February 10, 2022:

- **Liquidia** relied on 0.6 mL/min rate (*e.g.*, Reply at 12)
- **Dr. Hill** relied on 0.6 mL/min rate (*e.g.*, EX1106, ¶61)
- **Dr. Gonda** relied on 0.6 mL/min rate (*e.g.*, EX1107, ¶53)

Liquidia continued relying upon 0.6 mL/min

Sources: Paper No. 44, 12, 15; EX1086; EX1087; Paper No. 64, 2; EX1106, ¶61; EX1107, ¶53.

Calculation #1: Dr. Gonda's Alleged "Average" Rate Is Misleading

- Dr. Gonda asserts an "average" rate of 0.6 mL/min
- But:
  - He ignores true variation in <u>measured</u> rate of 0.22-1.14 mL/min
  - One manufacturer, limited number of devices
  - He did not search for and review data for all ultrasonic nebulizers, or all nebulizers available at the time

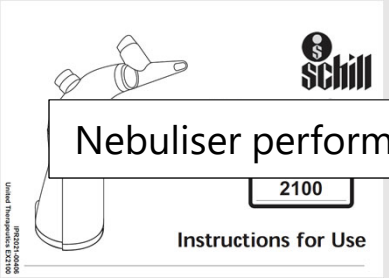
Dr. Gonda's references, if anything, show variation

- EX1097
  - 1987, not 2006
  - 0.33 mL/min
- EX1098
  - 1992
  - 0.22-0.68 mL/min
- EX1099
  - 1990
  - 0.67-1.14 mL/min

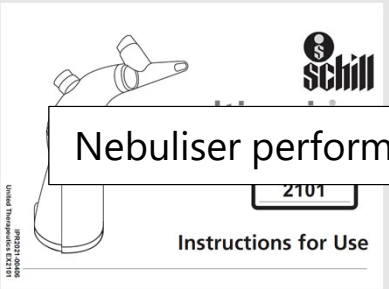
Sources: Paper No. 55, 13-14; EX1097; EX1098; EX1099; EX1107, ¶¶ 25, 33; EX2097, 160:12-17.

Calculation #1: Real Rates Don't Match Manual Output Rates

Manual Rates

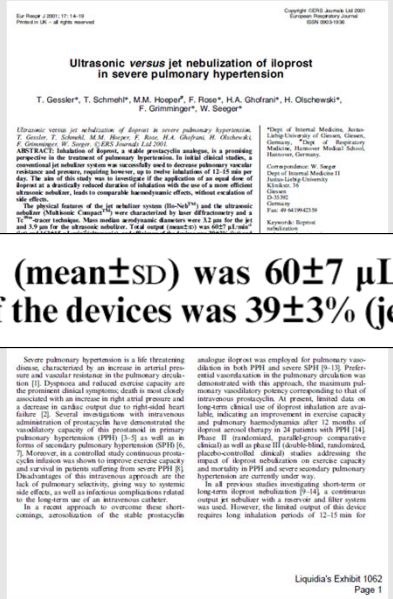


Nebuliser performance: approx. 0.5 ml/min



Nebuliser performance: approx. 0.6 ml/min

Tested Rate



Ultrasonic *versus* jet nebulization of iloprost in severe pulmonary hypertension

T. Gessler*, T. Schmehl*, M.M. Hoeper#, F. Rose*, H.A. Ghofrani*, H. Olschewski*, F. Grimminger*, W. Seeger*

Liquidia's Exhibit 1062
Page 1

Total output (mean±SD) was 60±7 µL·min^{-1} (jet) and 163±15 µL·min^{-1} (ultrasonic), and efficiency of the devices was 39±3% (jet)

=0.163 mL/min

- POSA would not rely on manual rates
- Manual output rates do not "account for" all variables as Liquidia asserts

Sources: Paper No. 55, 14-15; EX1062; EX2100; EX2101; EX2099, 173:19-24.

Calculation #1: Gonda Would Call Manufacturer About Output Rates

Dr. Gonda:

Q. Would you understand that as describing the nebulizer output for the Multisonic Infracontrol as 0.5 milliliters of drug solution per minute?

A. I would have probably asked the manufacturer how they measure it.

- Dr. Gonda admitted he would ask the manufacturer how output rates were calculated

Sources: Paper No. 55, 14-15; EX1062; EX2100; EX2101; EX2099, 173:19-24.

Calculation #1: Claim That Rates "Account For" All Variables—Not Credible

Gonda:

28.8 µg. The use of the output rate provided in the OptiNeb manual takes into account all material that is lost before reaching the mouthpiece which makes Professor McConville's argument that "the emitted dose (or 'delivered dose') will be less than the nominal or metered dose, as drug can be lost along the way" irrelevant (Ex. 2053 (McConville Declaration) at ¶ 40) as the output is the amount arriving at the mouthpiece after all the losses inside the nebulizer and connecting equipment occurred. The point being that both of these approaches (using typical

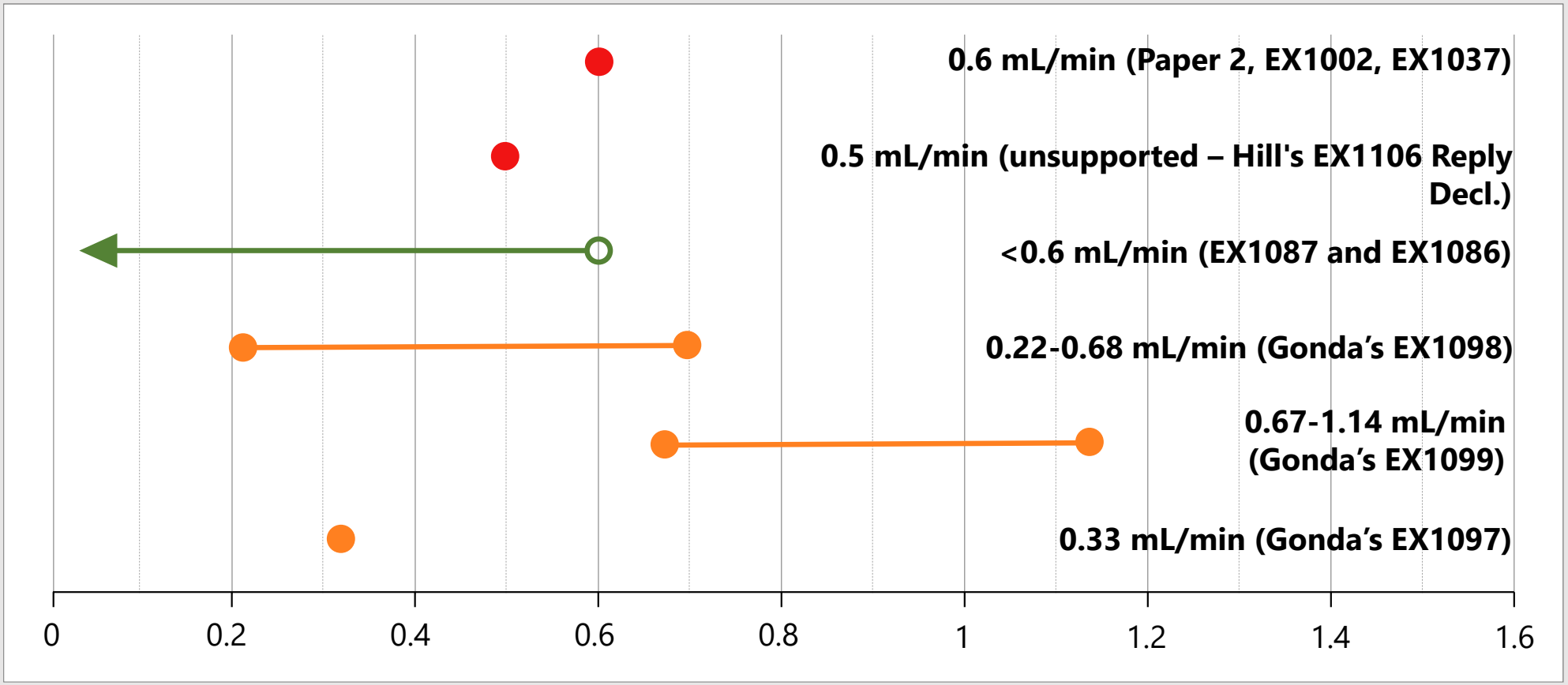
between the mouth and the lung in the oropharynx. Using the output rate already takes into account the losses all the way from the volume of the solution placed in the nebulizer to the point where the aerosol is exiting the mouthpiece. Using the

Hill:

time). Dr. Waxman again contends that a POSA would need to account for numerous variables such as gas flow and pressure (Ex. 2052, ¶ 66), but as I explained above, this argument is flawed because POSAs in 2006 would not have accounted for these variables in clinical practice, and in any event would have understood that the prior art references already accounted for such variables. *See* ¶ 44 above.

Sources: EX1106, ¶60; EX1107, ¶¶ 24, 30.

Calculation #1: Output Rate Variation Precludes Estimate In JESC



Sources: Paper 2, 23; EX1002, ¶67; EX1037, 28; EX1086; EX1087; EX1097; EX1098; EX1099; EX1106.

1 Volume Flaws

2 Rate Flaws

3 Efficiency Flaws

Calculation #1: Literatures Shows Wide Variety Of Efficiencies

Dr. McConville:

58. Testing is required or appropriate because so many factors bear on the output and devices can have a wide variety of efficiencies, varying by about 10x (i.e., about 9 to 90%). *See, e.g.*, EX2077 (Rau 2004) at 5 (Table 1) (describing in vitro testing showing that, across five nebulizers, the total inhaled dose varied from about 9% to 39% of the nominal dose); EX1066 at 1(estimating the dose delivered to the mouthpiece of the nebulizer at 43% and 39% albuterol based on "in vitro conditions"); EX1083 (Ventavis® Label) at 10 (describing delivered dose as 2.5 mcg out of 10, which is 25%); EX1062 (Gessler) at 2-3 (describing delivered doses of 39% for a jet nebulizer by Nebu-Tec and 86% for a nebulize by Schill Company); EX2078 (Rau 2005) at Fig. 19 (showing in vitro albuterol dispositions varying from 13% to 34% across three devices); EX2075 (Brun) at 7 ("[A]verage lung deposition for nebulizer therapy of only 10% is rather poor.").

Performance Comparison of Nebulizer Designs:
Constant-Output, Breath-Enhanced, and Dosimetric

Joseph L Rau PhD RRT FAA

Table 1. Aerosol Deposition and Loss, and Nebulization Time With 5 Nebulizer Brands*

	Misty-Neb	SideStream	Pari LCD	Circulaire	AeroEclipse
Total inhaled (%)	17.2 ± 0.4†	15.8 ± 2.8†‡	15.2 ± 4.2†‡	8.7 ± 1.0‡	38.7 ± 1.3
Inhalation filter (%)	14.4 ± 0.5†§	14.7 ± 2.7†	13.3 ± 4.2†§	7.4 ± 1.0§	34.2 ± 1.3
Exhaled to ambient (%)	26.8 ± 0.7	17.3 ± 0.4	18.3 ± 0.8	12.3 ± 0.8	6.6 ± 3.1
Deposited in nebulizer apparatus (%)	52.3 ± 0.6	63.4 ± 3.0	62.5 ± 4.0	75.8 ± 0.5	51.0 ± 2.1
Remained in unit-dose bottle (%)	3.7 ± 1.1	3.6 ± 0.5	4.1 ± 0.6	3.0 ± 0.4	3.7 ± 0.6
Nebulization time (min)	11.9 ± 0.3	9.5 ± 0.1	8.4 ± 1.2	7.0 ± 0.5	14.4 ± 1.1

*The percent values represent percent of total dose. The inhalation filter percentage is a subset of the total inhaled percentage; specifically, the inhalation filter percentage equals the total inhaled minus the amount deposited in the throat. Subsets of nebulizer brands with no significant differences ($p < 0.05$) based on follow-up comparisons are indicated for total inhaled percentage and inhalation filter percentage. Nebulization time was until sputter.
†No significant difference between Misty-Neb, SideStream, and Pari LCD
‡No significant difference between SideStream, Pari LCD, and Circulaire
§No significant difference between Misty-Neb, Pari LCD, and Circulaire

Introduction

Gas-powered jet nebulizers are commonly used for delivering medications in the clinical and home-care settings.

Over the past few years nebulizer design changes have created nebulizer categories, termed constant-output, breath-enhanced, and dosimetric.[1] Constant-output nebulizers are the traditional T-piece nebulizers that generate aerosol constantly, during the inhalation, exhalation, and breath-hold. With constant-output nebulizers some of the aerosol is lost during exhalation, which causes release of aerosol to the ambient air through the expiratory limb of the T-piece.[2–4] Constant-output nebulizers have been criticized as unreliable and inefficient, because a low percentage of the dose reaches the patient.[5–7] A length of large-bore tubing is usually attached to the expiratory side of the constant-output nebulizer T-piece, to reduce drug loss and

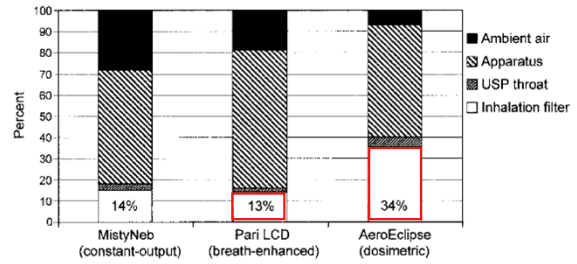


Fig. 19. In vitro disposition of albuterol with 3 types of nebulizer: constant-output (Misty-Neb), breath-enhanced (Pari LCD), and dosimetric (AeroEclipse). USP = United States Pharmacopoeia. (Based on data from Reference 43.)

2004 Philip Kittredge Memorial Lecture

The Inhalation of Drugs: Advantages and Problems

Joseph L Rau PhD RRT FAARC

Inhalation is a very old method of drug delivery, and in the 20th century it became a mainstay of respiratory care, known as aerosol therapy. Use of inhaled epinephrine for relief of asthma was reported as early as 1929, in England. An early version of a dry powder inhaler (DPI) was the

Respiratory Care • March 2005 Vol 50 No 3

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IPR2021-00406
United Therapeutics EX2078

Sources: EX2053 ¶58; EX2077, 5; EX2078, 12.

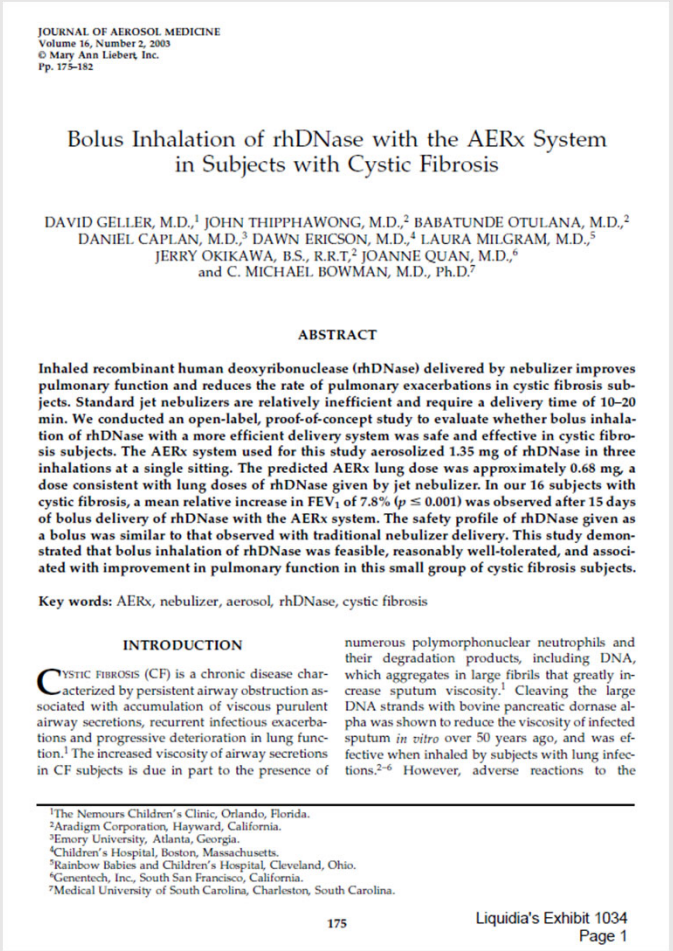
Calculation #1: Dr. Hill Assumes 50% Loss Rate

90 µg still would have been obvious. Dr. Waxman never identifies a specific amount of drug that he alleges is lost between the loaded dose and the mouthpiece, but even assuming that a high percentage, such as 50%, of the drug is lost in this process, Voswinckel JESC still renders obvious the claimed range. For example, in my First Declaration, I assumed inhalation of at least 1 mL of the provided concentrations of drug. Ex. 1002, ¶¶ 65, 99. Even assuming for the sake of argument that the 16, 32,

- No cited source for 50% assumption
- No cited source for later 75% assumption, either

Source: EX1106, ¶41.

Calculation #1: Dr. Hill Ignored Delivery Efficiencies Of 10-20%



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Pp. 175–182

Bolus Inhalation of rhDNase with the AERx System in Subjects with Cystic Fibrosis

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ABSTRACT

Inhaled recombinant human deoxyribonuclease (rhDNase) delivered by nebulizer improves pulmonary function and reduces the rate of pulmonary exacerbations in cystic fibrosis subjects. Standard jet nebulizers are relatively inefficient and require a delivery time of 10–20 min. We conducted an open-label, proof-of-concept study to evaluate whether bolus inhalation of rhDNase with a more efficient delivery system was safe and effective in cystic fibrosis subjects. The AERx system used for this study aerosolized 1.35 mg of rhDNase in three inhalations at a single sitting. The predicted AERx lung dose was approximately 0.68 mg, a dose consistent with lung doses of rhDNase given by jet nebulizer. In our 16 subjects with cystic fibrosis, a mean relative increase in FEV_1 of 7.8% ($p \leq 0.001$) was observed after 15 days of bolus delivery of rhDNase with the AERx system. The safety profile of rhDNase given as a bolus was similar to that observed with traditional nebulizer delivery. This study demonstrated that bolus inhalation of rhDNase was feasible, reasonably well-tolerated, and associated with improvement in pulmonary function in this small group of cystic fibrosis subjects.

Key words: AERx, nebulizer, aerosol, rhDNase, cystic fibrosis

INTRODUCTION

Cystic fibrosis (CF) is a chronic disease characterized by persistent airway obstruction associated with accumulation of viscous purulent airway secretions, recurrent infectious exacerbations and progressive deterioration in lung function.[1] The increased viscosity of airway secretions in CF subjects is due in part to the presence of numerous polymorphonuclear neutrophils and their degradation products, including DNA, which aggregates in large fibrils that greatly increase sputum viscosity.[1] Cleaving the large DNA strands with bovine pancreatic dornase alpha was shown to reduce the viscosity of infected sputum *in vitro* over 50 years ago, and was effective when inhaled by subjects with lung infections.[2–6] However, adverse reactions to the

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[2]Aradigm Corporation, Hayward, California.
[3]Emory University, Atlanta, Georgia.
[4]Children's Hospital, Boston, Massachusetts.
[5]Rainbow Babies and Children's Hospital, Cleveland, Ohio.
[6]Genentech, Inc., South San Francisco, California.
[7]Medical University of South Carolina, Charleston, South Carolina.

Liquidia's Exhibit 1034
Page 1

> Conventional nebulizers typically have a delivery efficiency of only 10–20%.[16] In a previous scintigraphic study[17] of inhaled rhDNase, the nebulizers delivered 0.16–0.78 mg of the 2.5-mg loaded dose into the lung. This represents a delivery efficiency of only 6–31%.

Q. So you did not review the article by Cipolla when preparing your reply declaration?

A. No, I didn't, but I know well that the efficiency of delivery of nebulizers – aerosolized delivery from nebulizers has variable efficiency in different reports in the literature, 20 percent would be that the lower end of the range, but there certainly is a – what sounds like a relatively low efficiency of delivery of these devices as well now.

Calculation #1: Dr. Hill Acknowledges Wide Range of Nebulizer Efficiency

Q. So you don't have any personal knowledge dating back to that 2004 time frame, approximately, about what the authors' concerns were or why they selected any given nebulizer; correct?

A. I don't have any personal knowledge, no, but as a POSA with experience using nebulizers, you know, I know that there is a wide range that, as I stated earlier in my testimony, in terms of efficiency between nebulizers, and I know it would be important for authors of a study like this to select a device that they could rely on to deliver a reliable dose at a reliable delivery rate.

Sources: Paper No. 64, 2; EX1034, 3; EX2108, 36:17-37:1, 47:7-20.

Calculation #1: Dr. Gonda's References And Testimony Show Efficiency Variation

- Accuneb label shows efficiencies of 39-43%
- Gessler shows delivered dose efficiency for one specific drug and nebulizer of 86%
  - Gonda admits some nebulizers are lower than 86%

Q. But as far as my question, some ultrasonic nebulizers in 2006, would have had an efficiency of lower than 86 percent; correct?

A. Yes.

AccuNeb (albuterol sulfate) Inhalation Solution is supplied in two strengths in unit dose vials. Each unit dose vial contains either 0.75 mg of albuterol sulfate (equivalent to 0.63 mg of albuterol) or 1.50 mg of albuterol sulfate (equivalent to 1.25 mg of albuterol) with sodium chloride and sulfuric acid in a 3-mL isotonic, sterile, aqueous solution. Sodium chloride is added to adjust isotonicity of the solution and sulfuric acid is added to adjust pH of the solution to 3.5 (see HOW SUPPLIED).

AccuNeb (albuterol sulfate) Inhalation Solution does not require dilution prior to administration by nebulization. For AccuNeb, like all other nebulized treatments, the amount delivered to the lungs will depend on patient factors, the jet nebulizer utilized, and compressor performance. Using the Pari LC Plus™ nebulizer (with face mask or mouthpiece) connected to a Pari PRONEB™ compressor, under in vitro conditions, the mean delivered dose from the mouth piece (% nominal dose) was approximately 43% of albuterol (1.25 mg strength) and 39% of albuterol (0.63 mg strength) at a mean flow rate of 3.6 L/min. The mean nebulization time was 15 minutes or less. AccuNeb should be administered from a jet nebulizer at an adequate flow rate, via a mouthpiece or face mask (see DOSAGE AND ADMINISTRATION).

Sources: Paper No. 55, 16 (citing EX1066, right column); EX1066; EX2099, 158:24-159:1,159:3.

Calculation #1: Formulations Affect Efficiency

The three drug solutions for inhalation used in the study were: albuterol sulfate 2.5 mg/3 mL (Proventil® Inhalation Solution 0.083%, Schering-Plough), cromolyn sodium 20 mg/2 mL (Intal® Nebulizer Solution 20mg/2mL, Aventis), and ipratropium bromide 0.5 mg/2.5 mL (Ipratropium Bromide Inhalation Solution 0.02%, RxElite). A pre-production MyNeb was filled with one

Table 1

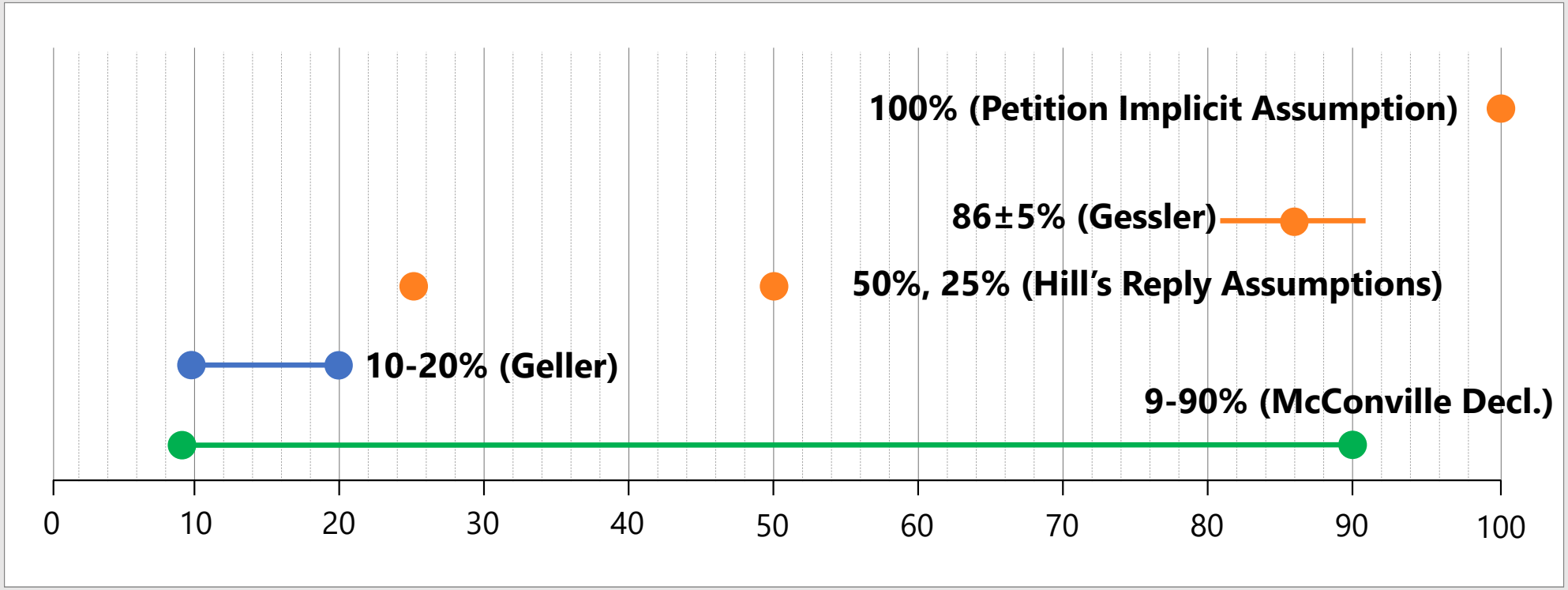
MyNeb™ Performance.

	Albuterol Sulfate			Cromolyn Sodium			Ipratropium Bromide		
	Mean (mg)	SD (mg)	% CV	Mean (mg)	SD (mg)	% CV	Mean (mg)	SD (mg)	% CV
Amount of Drug Exiting Nebulizer (mg)	1.73	0.07	4.04	10.3	0.3	2.63	0.3	0.03	8.32
Amount in Fine Particle Dose (mg)	1.11	0.01	1.11	6.8	0.7	9.63	0.2	0.02	12.08
% Drug in Fine Particle Dose	64.43	1.95	3.02	66.32	5.67	8.55	63.77	2.86	4.49
MMAD	3.28	0.21	6.46	3.11	0.27	8.74	3.39	0.20	5.75
GSD	1.75	0.05	2.86	1.90	0.05	2.79	1.86	0.02	0.82

- Lieberman 2006 shows variation from 52%-69% using the same nebulizer

Sources: Paper No. 55, 15-16; EX2103 (Lieberman).

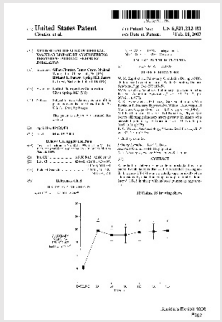
Calculation #1: Nebulizer Efficiencies Vary Widely

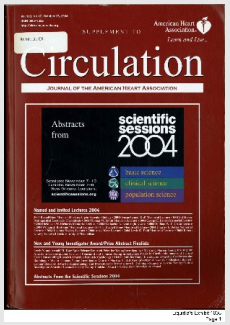


Sources: Paper 2; Ex. 1106, ¶¶ 41, 42; EX2053; EX1062, 16.

Calculation #1: Liquidia's References Do Not Teach 15-90 µg Dose

No express teaching of claimed dose





Flaws in attempts to calculate claimed dose

- JESC fill and residual volume unknown
- JESC rate with treprostinil unknown
- JESC efficiency unknown
- Wide variation in fill volumes, rates, efficiencies
- POSA could not reliably calculate the dose used in JESC

Source: Paper 55, 11-22.

Flawed Calculation #2 – ’212 Patent + Remodulin Label

POSA Would Not Assume Conversion From Daily To 4x/Day Dosing

Dr. Waxman explains that the effects of continuous and bolus dosing are different

59. Moreover, as mentioned above, the pharmacokinetic effect of a given dose of a pulmonary drug administered by continuous intravenous infusion over a 30-minute time interval (or 60 or 90-minute interval) is completely different from the effect of the same pulmonary drug administered as a bolus or in a few breaths, such as with a metered dose inhaler or dry powder inhaler. In the case of claim 1 of the '793 patent, 15 to 90 micrograms of treprostinil are delivered in 1 to 3 breaths, which the POSA would expect would to lead to more drug potentially entering systemic circulation (due to spillover from the lungs into systemic circulation) than is the case when much smaller amounts per breath are delivered to the lungs over 30-90 minutes.

51. A POSA would understand that the way a drug affects the body, including the lungs, is different when a drug is administered over 30-90 minutes at a low rate, versus over a fraction of a minute at a high rate (*e.g.*, almost a bolus dose). In particular, a POSA would understand that at low rates of administration, the lungs may absorb all of the drug, and the pharmacokinetics (*e.g.*, blood levels) may never spike; rather, plasma levels of the drug are more likely to slowly rise to a steady state. With a bolus dose, or one inhaled in only 1 to 3 breaths, a POSA could expect a faster and higher spike in blood levels. And with inhalation administration, there could be spillover from the lungs (site of absorption by the body) into systemic circulation; such spillover would be much less likely with a slower rate of administration (for example, from a lengthier continuous nebulization).

Sources: Paper No. 55, 20; EX2052, ¶¶ 51, 59.

The Petition's Calculation Was Flawed

- The Petition asserted that applying the 212 patent's "10-50%" ratio to IV doses of Remodulin (intravascular treprostinil) "confirmed" Dr. Hill's calculated JESC doses
- The Board disagreed

> On the present record, we determine that Patent Owner is correct that Petitioner's second calculation fails to show a single event dose of between 15 and 90 µg of treprostinil. Petitioner's second calculation relies on the teaching of the '212 patent that the dose of treprostinil delivered by inhalation should be "10–50%" of the dose required for intravascular delivery. Ex. 1006, 8:8–12; *see* Pet. 38–39. Petitioner and Dr. Hill provide 1008, 3. Even at the high end of the range that emerges from Petitioner's second calculation, one fourth of the total daily dose is less than the fifteen-microgram lower end of the claimed range.

Sources: Paper No. 2, 38-39; Paper No. 18, 29-30.

Liquidia's New '212 Patent Arguments Remain Flawed (Even If Considered)

Dr. Hill presents new arguments:

- Divides by four
- Increased Remodulin doses
- Higher patient masses (kg)
- New, uncited formulas

The arguments remain flawed:

- Hill admits 10-50% is potentially inaccurate and misleading
- POSA would not rely on 10-50% fraction
  - Broad, imprecise
  - Sheep data
  - Chemically induced PH
- JAHA does not define 4/day as a hard and fast rule

Sources: e.g., EX1002; EX1106, ¶¶53-55; EX2055, 102:23-103:10, 103:21-104:9, Paper No. 55 at 18-19.

Dr. Hill Undermines The 10-50% Ratio He Relies On

Q. And from that teaching, you believe or apply this 10 to 50 percent as being an accurate measure of the relative potency of Treprostinil in aerosolization versus intravascular administration, correct?

A. I'm not sure about the accuracy. This is what we were provided with, and this is based upon the experiment they did in sheep that is described here. But it's what we have to go on.

Q. You agree that comparing blood levels during infusion and after inhalation may be misleading, right?

A. Yes.

Q. So you'd agree that clinicians need to rely upon clinical assessment as proof of response to therapy, not rough measures of relative potency between intravascular and aerosolized delivery, right?

A. I think the response, in this case the response of the pressures in the lung in the sheep model, it's important to show the change in the pulmonary pressure that any level that you can measure. So it can be misleading to rely on levels, yes – blood levels, circulating levels.

Source: EX2055, 102:23-103:10, 103:21-104:9.

Comparing a Daily Dose to a Single Event Dose is Like Comparing Apples to Oranges

Dr. Hill (Petitioner's Expert):

Q. But that 15 to 90 microgram range is the single-event dose, not the daily dose, right?

A. That's correct.

Q. And so those are apples and oranges, aren't they?

A. Yes, I think so. If I might add, the 1.25 is a starter dose, and it's a dose that no one would be kept on for any length of time. When we start this drug, we anticipate that we're going to go up gradually on the dose.· Sometimes to manifold what this initial dose is. So as you go up, you're certainly going to cross the range that you would use with the inhaled dose.

Source: EX2055, 100:12-17.

POSA Would Not Administer A Dose Calculated From Sheep Data

Sandifer teaches that human doses ≠ sheep doses

how the drug acts. To achieve an effect in sheep, it was necessary to administer doses of treprostinil that were much higher than those used in treating patients, regardless of the route of delivery. Whether this is due to differences in species or a requirement for higher doses of vasodilator to overcome thromboxane-induced vasoconstriction of the degree we produced experimentally is not clear.

arterial oxygen saturation. These patients were evaluated over 12 wk of therapy, so it is difficult to compare these results with our acute model of pulmonary hypertension with one-time dosing of therapy in otherwise normal sheep with acute pulmonary vasoconstriction.

JAHA involved patients with severe PH, not chemically induced

Objective: To evaluate the effects of inhaled TRE on pulmonary hemodynamics and gas exchange in severe pulmonary hypertension (PH) and to assess safety, tolerability and clinical efficacy in patients with severe PH. **Background:** TRE is a stable prostacyclin analogue that has

JAHA

It has been discovered that aerosolized UT-15 has both greater potency and efficacy relative to attenuating chemically induced pulmonary hypertension as shown by an increase in pulmonary vascular resistance. Furthermore,

'212

Sources: Paper No. 55, 18; EX1006, 8:5-8; EX1008, 3; EX2087, 5.

New Reply Argument Based On McLaughlin Also Fails

Journal of Cardiovascular Pharmacology™
41:293–299 © 2003 Lippincott Williams & Wilkins, Inc., Philadelphia

Efficacy and Safety of Treprostinil: An Epoprostenol Analog for Primary Pulmonary Hypertension

*Vallerie V. McLaughlin, †Sean P. Gaine, ‡Robyn J. Barst, §Ronald J. Oudiz, ‖Robert C. Bourge, ¶Adaani Frost, #Ivan M. Robbins, **Victor F. Tapson, ††Michael D. McGoon, ‡‡David B. Badesch, §§Jeff Sigman, §§Robert Roscigno, §§Shelmer D. Blackburn, §§Carl Arneson, ‖Lewis J. Rubin, and *Stuart Rich, on behalf of the Treprostinil Study Group

*Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois; †Johns Hopkins Hospital, Baltimore, Maryland; ‡Columbia University College of Physicians and Surgeons, New York, New York; §Harbor-UCLA Medical Center, Los Angeles, California; ‖University of Alabama at Birmingham, Birmingham, Alabama; ¶Methodist Hospital, Baylor Medical College, Houston, Texas; #Vanderbilt University Medical Center, Nashville, Tennessee; **Duke University Medical Center, Durham, North Carolina; ††Mayo Clinic, Rochester, Minnesota; ‡‡University of Colorado Health Sciences Center, Denver, Colorado; §§United Therapeutics Corporation, Research Triangle Park, North Carolina; and ‖University of California at San Diego, San Diego, California, U.S.A.

Summary: Intravenous epoprostenol is currently FDA approved for management of primary pulmonary hypertension, but it requires intravenous infusion and is associated with adverse effects. The objective of this study was to evaluate the effects of an epoprostenol analog, treprostinil, for management of pulmonary hypertension. Ten tertiary care academic institutions with pulmonary hypertension programs participated in these pilot trials. In the first trial, intravenous epoprostenol and intravenous treprostinil were compared. In the second trial, intravenous treprostinil and subcutaneous treprostinil were compared. In the third trial, subcutaneous treprostinil was compared with placebo infusion during an 8-week period. Intravenous epoprostenol and intravenous treprostinil resulted in a similar reduction in pulmonary vascular resistance acutely (22% and 20%, respectively). Intravenous treprostinil and subcutaneous treprostinil also demonstrated comparable short-term decrease in pulmonary vascular resistance (23% and 28%, respectively). The placebo-controlled 8-week trial demonstrated a mean improvement of 37 ± 17 m as measured by the 6-minute walk distance in patients receiving treprostinil compared with a 6 ± 28 m reduction in those receiving placebo. There were trends toward an improvement in cardiac index and pulmonary vascular resistance index in the treprostinil group. Subcutaneous treprostinil has favorable hemodynamic effects when given acutely and in the short term. Treprostinil can be given safely to an ambulatory patient with a novel subcutaneous delivery pump system. **Key Words:** Pulmonary arterial hypertension—Hemodynamics—Epoprostenol—Prostacyclin.

Received December 3, 2001; accepted July 16, 2002.
Supported by United Therapeutic Corporation, Research Triangle Park, North Carolina.
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<u>Procedural Problems</u>

- Not presented in Petition
- Not a basis for obviousness – presented only as "support[]"

<u>Substantive Problems</u>

- Same issues with reliance on 10-50% number
- Same problems with converting IV dose to single event dose
- Waxman: IV and bolus dosing are very different

Sources: EX1106, 48-49; EX2036, 295; EX2055, 108:22-109:24; EX1108.

Calculation #2: No Dose With Reasonable Expectation Of Success

POSA would not rely on sheep data conversion factor

- Calculation #2 relies on broad, approximate 10-50% conversion from '212 patent/sheep data
- Hill admits 10-50% may be inaccurate and misleading
- Claim requires treating a patient with reasonable expectation of success
- Day-long IV dosing and bolus dosing are very different
- POSA would not treat a patient based on sheep data back-of-the-envelope math

Sources: Paper No. 29, 24; Paper No. 55, 18; EX1002; EX1106; EX2055, 102:23-103:10, 103:21-104:9.

Flawed Calculation #3 – ’212 Patent PVD

The Board Did Not Credit Liquidia's Footnote Argument

Liquidia did not argue that the '212 patent's broad PVD range rendered the claimed dose obvious

[13] In addition, the '212 Patent discloses that "[i]n the case of treating peripheral vascular disease . . . [,] the dosage for inhalation . . . should be sufficient to deliver an amount that is equivalent to a daily [intravascular] infusion dose in the range of 25µg to 250mg." EX1006, 5:54-62; *see also id.*, Figs. 16, 18. By teaching that only 10-50% is needed for inhalation (*id.*, 8:5-12), the '212 Patent discloses that the effective dosage of inhaled treprostinil for treating peripheral vascular disease would be 2.5µg (micrograms) to 125mg (milligrams). This encompasses the full 15 to 90 micrograms claimed by the '793 Patent. Accordingly, given the fact that the '212 Patent is directed to methods of treating both pulmonary hypertension and peripheral vascular disease (*see id.*, 13:26-14:29, claims 6 and 9), a POSA would understand that an inhaled dosage of 15 to 90 micrograms of treprostinil for treatment of pulmonary hypertension would be equally possible. EX1002, ¶100n4.

The Board addressed Liquidia's "two" calculations, not three

As discussed more fully below, Petitioner and its declarants provide two separate calculations to attempt to establish that the prior art taught or suggested the range of treprostinil doses recited in the challenged claims. Pet. 23, 38–39; Ex. 1002 ¶¶ 65–67, 99–100; Ex. 1004 ¶¶ 56–57. One of these calculations begins with the intravascular dose on the FDA label for Remodulin and adjusts that for the '212 patent's teaching that inhalation requires 10–50% the dose that intravascular administration requires. Pet. 38–39. This calculation does not rely on Exhibit 1037 at all. *Id.*

The other calculation begins with Voswinckel JESC's teaching that patients were administered a nebulized solution over six minutes with a treprostinil concentration of 16, 32, 48, or 64 µg/mL, then multiplies that concentration by the volume of solution that would have been nebulized over a six-minute period. Pet. 23. The evidence supporting that volume of solution comes from Petitioner's declarants. *Id.* (citing Ex. 1002 ¶¶ 65, 67;

Sources: Paper No. 2, 39-40, n.13; Paper No. 18, 23-24.

The '212 Patent's PVD Range Is So Broad It Teaches Nothing

Dr. Hill relies on:

This invention further relates to delivering a benzindene prostaglandin and/or its salts or esters by inhalation for applications where inhalation delivery is appropriate for the treatment of that particular condition. Benzindene prostaglandins, including UT-15 and its salts or esters, have been shown to be useful for multiple applications. For example, UT-15 has been shown to exhibit a potent anti-aggregatory action on blood platelets, and therefore has a particular utility in mammals as an anti-thrombotic agent. Further known uses of UT-15 include treatment of peripheral vascular disease (covered in co-pending application Serial No. 09/190,450, now U.S. Pat. No. 6,054,486, the entire contents of which are incorporated by reference herein). In the case of treating peripheral vascular disease by inhalation of a benzindene prostaglandin of the present invention, the dosage for inhalation, taking into account that some of the active ingredient is breathed out and not taken into the bloodstream, should be sufficient to deliver an amount that is equivalent to a daily infusion dose in the range of 25 μg to 250 mg; typically from 0.5 tg to 2.5 mg, preferably from 7 μg to 285 μg, per day per kilogram bodyweight. For example, an intravenous dose in the range 0.5 μg to 1.5 mg per kilogram bodyweight per day may conveniently be administered as an infusion of from 0.5 ng to 1.0 μg per kilogram bodyweight per minute. A preferred dosage is 10 ng/kg/min.

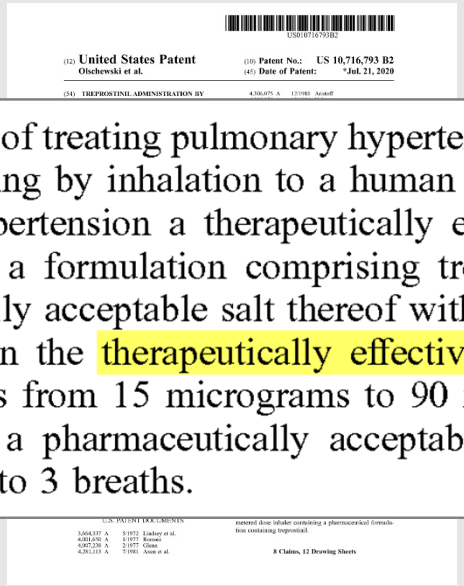
- POSA would not rely on the PVD range
  - Upper is 50,000 times larger than lower endpoint of range
  - Different disease – peripheral vascular disease versus pulmonary hypertension
- '212 patent regarding PVD would not direct POSA to 15-90 µg range for PH

Based on my knowledge and experience, a POSA would not use this data to infer or calculate delivered doses for the treatment of pulmonary hypertension because dosing is quite different for treatment of different conditions.

Sources: EX1006, 5:42-67; EX2052, ¶¶52, 61.

Grounds 1 & 2:
Dr. Hill: Liquidia's References Do Not Show "Therapeutically Effective" Limitation

Claim 1 Requires a Single Event Dose That is "therapeutically effective"



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

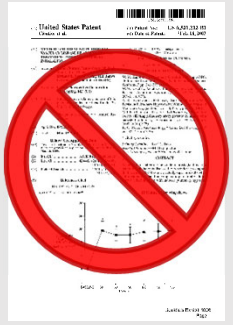
(10) Patent No.: US 10,716,793 B2
(45) Date of Patent: *Jul. 21, 2020

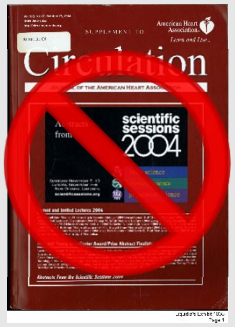
(54) TREPROSTINIL ADMINISTRATION BY

1. A method of treating pulmonary hypertension comprising administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof with an inhalation device, wherein the therapeutically effective single event dose comprises from 15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 3 breaths.

8 Claims, 12 Drawing Sheets

- Ground 1: '212 + JESC + JAHA
- Ground 2: '212 + JESC
- Dr. Hill does not believe '212 patent, JESC, or JAHA include a "therapeutically effective single event dose"





Sources: EX1001, claim 1; EX1006; EX1007; EX1008; EX2096, 134:6-135:9, 181:20-185:15; Paper 55, 22-23.

Dr. Hill: Hemodynamics Does Not Disclose "therapeutically effective"

Liquidia and Dr. Hill told the PTAB that no construction was required (EX2055, 43:13-24)…

> **V. CLAIM CONSTRUCTION UNDER 37 C.F.R. § 42.104(b)(3)**
>
> For purposes of resolving this IPR, Petitioner does not believe construction of any claim term is required. All terms should be given their plain and ordinary meaning in the art as of May 15, 2006. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-1313 (Fed. Cir. 2005); 37 C.F.R. § 42.100(b).

…But Dr. Hill adopted and presented narrowing constructions in district court

Q. Now, you conclude – you conclude that hemodynamic data is not sufficient to demonstrate therapeutic effectiveness of a single-event dose, is that right, for infringement purposes?

A. Yes, that's correct.

Q. … [W]ould you agree with me that in order to have a therapeutic effective single-dose, that you would want to see a hemodynamically effective single-event dose?

A. I don't think that an acute hemodynamic effect establishes therapeutic efficacy.

Sources: Paper No. 2, 12-13; EX2096, 131:7-12, 135:3-9; *see also* EX2096, 82:22-83:5.

Under Dr. Hill's Opinion, The '212 Patent Is Not "therapeutically effective"

The '212 patent only shows hemodynamic parameters

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a graph of pulmonary vascular resistance (cmH_2O*min/liter) intravenously induced by U44069 over time (min).

FIG. **2** describes the effects of a high dose of UT15, given as an aerosol, on the hemodynamic variables of the sheep. Specifically, FIG. **2** depicts the effects of the aerosolized UT15 administered to the sheep intravenously induced with U44069 on systemic arterial pressure (PSA or PSYS); on pulmonary arterial pressure (PPA); and pulmonary vascular resistance (PVR), respectively.

FIG. **3** is the dose-response effect of intravenously infused UT15 and aerosolized UT15 on the heart rate during baseline conditions.

FIG. **4** is the dose-response effect of intravenously infused UT15 and aerosolized UT15 on the systemic arterial pressure during baseline conditions.

FIG. **5** is the dose-response effect of intravenously infused UT15 and aerosolized UT15 on the central venous pressure during baseline conditions.

FIG. **6** is the dose-response effect of intravenously infused UT15 and aerosolized UT15 on the pulmonary arterial pressure during baseline conditions.

FIG. **7** is the dose-response effect of intravenously infused UT15 and aerosolized UT15 on the left atrial pressure during baseline conditions.

FIG. **8** is the dose-response effect of intravenously infused UT15 and aerosolized UT15 on cardiac output during baseline conditions.

FIG. **9** is the dose-response effect of intravenously infused UT15 and aerosolized UT15 on pulmonary vascular resistance during baseline conditions.

FIG. **10** is the dose-response effect on the heart rate of intravenously infused UT15 and aerosolized UT15 during intravenously infused U44069.

FIG. **11** is the dose-response effect of intravenously infused and aerosolized UT15 on central venous pressure during intravenously infused U44069.

FIG. **12** is the dose-response effect of intravenously infused and aerosolized UT15 on systemic arterial pressure during intravenously infused U44069.

FIG. **13** is the dose-response effect of intravenously infused and aerosolized UT15 on pulmonary arterial pressure during intravenously infused U44069.

FIG. **14** is the dose-response effect of intravenously infused and aerosolized UT15 on left atrial pressure during intravenously infused U44069.

FIG. **15** is the dose-response effect of intravenously infused and aerosolized UT15 on cardiac output during intravenously infused U44069.

FIG. **16** is the dose-response effect of intravenously infused and aerosolized Ut15 on pulmonary vascular resistance during intravenously infused U44069.

FIG. **17** is the dose-response effect of intravenously infused and aerosolized UT15 on pulmonary vascular driving pressure (PPA minus PLA) during baseline-conditions.

FIG. **18** is the dose-response effect of intravenously infused and aerosolized UT15 on pulmonary vascular driving pressure (PPA-PLA) during intravenously infused U44069.

US006521212B1

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

(10) **Patent No.: US 6,521,212 B1**
(45) **Date of Patent: *Feb. 18, 2003**

(54) **METHOD FOR TREATING PERIPHERAL VASCULAR DISEASE BY ADMINISTERING BENZINDENE PROSTAGLANDINS BY INHALATION**

(75) Inventors: **Gilles Cloutier**; **James Crow**; **Michael Wade**, all of Chapel Hill, NC (US); **Richard E. Parker**, Spring Hill; **James E. Loyd**, Nashville, both of TN (US)

(73) Assignee: **United Therapeutics Corporation**, Silver Spring, MD (US)

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6,054,486 A * 4/2000 Crow et al.

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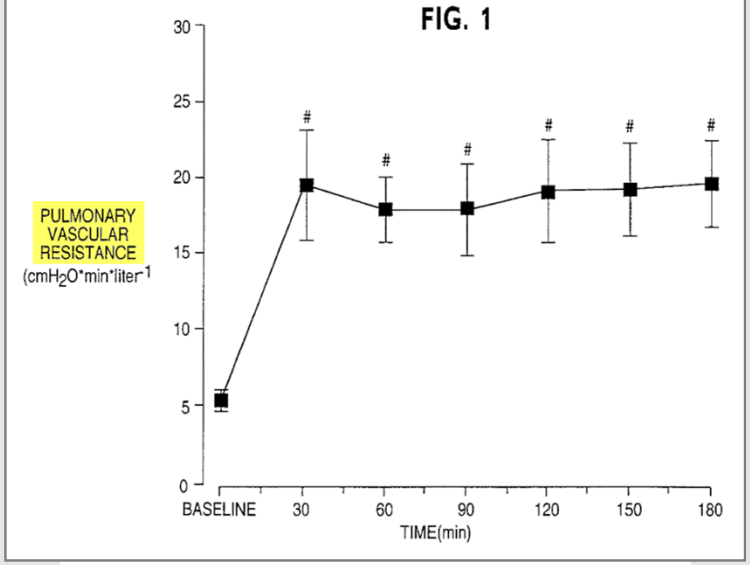
W. W. Fox et al., Pediatrics, "Pulmonary Hypertension in the Perinatal Aspiration Syndromes," vol. 59, No. 2, pp. 705–713 (1977).

FIG. 1



Liquidia's Exhibit 1006
Page 1

Sources: EX1006, 2, 21; Paper No. 55, 22-23.

Dr. Hill: JESC Does Not Disclose "therapeutically effective" Limitation

According to Dr. Hill, Voswinckel JESC lacks therapeutic effectiveness

Q. Are there any other reasons why the Voswinckel JESC approach would not infringe claim one?

A. Well, I don't think they have sufficient evidence here to demonstrate a potential for therapeutic efficacy. So it would fall short on that count.

Q. Do you see anything in Voswinckel JESC that in your mind supports a finding of a therapeutically effective single-event dose?

A. As I said, I would characterize it as hemodynamic effective, but I don't see anything that would meet my standard of therapeutic effectiveness.

Sources EX2096: 135:3-9, 135:17-18, 182:22-183:3; Paper 55, 22-23.

Dr. Hill: Cited JAHA's Compassionate Use Patients Only…

Inhaled Treprostinil Sodium (TRE) For the Treatment of Pulmonary Hypertension

Robert Voswinckel, Beate Enke, Andre Kreckel, Frank Reichenberger, Stefanie Krick, Henning Gall, Tobias Gessler, Thomas Schmehl, Markus G Kohstall, Friedrich Grimminger, Hossein A Ghofrani, Werner Seeger, Horst Olschewski; Univ Hosp Giessen, Giessen, Germany

Objective: To evaluate the effects of inhaled TRE on pulmonary hemodynamics and gas exchange in severe pulmonary hypertension (PH) and to assess safety, tolerability and clinical efficacy in patients with severe PH. **Background:** TRE is a stable prostacyclin analogue that has been approved for treatment of pulmonary arterial hypertension as a continuous subcutaneous infusion. Iloprost, another prostacyclin analogue, has been shown to be efficacious in a randomised controlled study as repetitive inhalation. **Methods**: In an open-label study a preservative free solution of inhaled TRE was applied to 17 patients with severe pulmonary hypertension during Swan-Ganz catheter investigation. Patients received a TRE inhalation by use of the pulsed OptiNeb® ultrasound nebulizer (3 single breaths, TRE solution 600 μg/ml). Hemodynamics were observed for 2 hours. Two patients with idiopathic PAH received compassionate treatment with 4 inhalations of TRE per day after the acute test. **Results**: Patients (male/female= 4/13) suffered from iPAH (n=5), PAH other (n=8) and CTEPH (n=4); PVR 948 ± 112 dyn*s*cm^{-5}, PAP 48.3 ± 2.7 mmHg, PAWP 8.9 ± 0.5 mmHg, CVP 10.8 ± 1.6 mmHg, CO 3.8 ± 0.3 l/min, SvO2 61.8 ± 1.8 %. TRE inhalation resulted in a sustained, highly pulmonary selective vasodilatation over 120 minutes. Maximum PVR decrease was -31.2 ± 4.5 % after 30 min. PVR and SVR at 120 minutes after inhalation were 89.2 ± 4.2 % and 101.0 ± 4.0 % of the baseline values, respectively. The AUC for the observation period (120min) was -22.9 ± 3.8 % for PVR and -4.9 ± 3.2% for SVR. The compassionate use patients have been treated for more than 3 months. In both patients NYHA class improved (from IV to III and from III to II), and six minute walk increased (from 0 m (bedridden) to 143 m, and from 310 m to 486 m, respectively). No side effects have been observed by the patients during long-term treatment. **Conclusion:** Inhaled TRE shows strong pulmonary selective vasodilatory efficacy with a long duration of effect following single acute dosing. Tolerability is excellent even at high drug concentrations and short inhalation times (3 breaths). Long-term treatment effects are very promising. The current results warrant controlled studies investigating this approach in a larger series of patients. Supported by Lung RX

Q. So the question, let me make it clear, is: I'm curious if you'd humor me, for you to point me to where Voswinckel JAHA and Voswinckel JESC you find support in your invalidity opinion for therapeutic effect of single-event dose?

A. Right. So if we look at Voswinckel JAHA, and that is abstract 1414, they describe two patients with idiopathic PAH who received compassionate treatment with four inhalations of three per day after the acute test, and they showed in these patients that it resulted in a sustained highly pulmonary selective vasodilation over 45 minutes and had been treated for more that three months.
In both patients, NYHA class improved by one class and no side effects had been observed. The six-minute walk distance improve from nothing to 143 meters and from 310 to 480 meters respectively. So these are long-term applications that show improvements in outcomes that I think establish at least potential for therapeutic effectiveness.

Sources: EX1008; EX2096, 134:6-135:2.

… But Dr. Hill Also Believes "single event dose" Means Once Per Day, Max

Hill Deposition

Q. … Do you read the claim, claim one of the '793 patent, as allowing for only one single-event dose per day?

A. Well, if I look at it and read it, you know, as stated, it says: Administration to a human with pulmonary hypertension with the therapeutically effective single-event dose, and it doesn't say anything about, you know, other doses. So I interpret that to say it's single-event dose.

Q. So only – so if – if I were as a person perhaps suffering from pulmonary hypertension, God forbid, if I were to take the LIQ861 product only once – more than once a day, then according to your interpretation of the claims, I would not be infringing that patent; is that right?

A. That's correct.

Q. So if a person does more than one administration in a day, they don't infringe this claim; correct?

A. That's correct.

Voswinckel JAHA

randomised controlled study as repetitive inhalation. **Methods**: In an open-label study a preservative free solution of inhaled TRE was applied to 17 patients with severe pulmonary hypertension during Swan-Ganz catheter investigation. Patients received a TRE inhalation by use of the pulsed OptiNeb® ultrasound nebulizer (3 single breaths, TRE solution 600 μg/ml). Hemodynamics were observed for 2 hours. Two patients with idiopathic PAH received compassionate treatment with 4 inhalations of TRE per day after the acute test. **Results**:

Hill Deposition

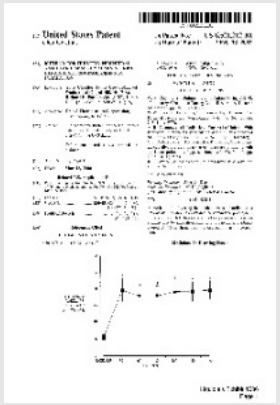
Regarding Voswinckel JAHA:

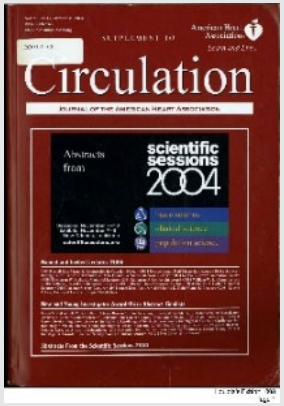
Q. And so there four inhalations of TRE per day after the acute test refers to four single-event doses of [t]reprostinil per day after the acute test; correct?

A. Yes.

Sources: EX1008; EX2096, 160:16-161:7, 163:12-15; EX2108, 41:19-23.

Liquidia's References Do Not Meet Claim 1, According To Dr. Hill





Therapeutically Effective	**Hill:** ✗	**Hill:** ✗	**Hill:** Compassionate use patients
single event dose			**Hill:** ✗

Sources: Paper No. 2, 34-35; EX1002, ¶147; EX2096, 82:22-83:5.

No Reasonable Expectation of Success

Bolus Dosing Can Result In Spillover

Dr. Waxman:

51. A POSA would understand that the way a drug affects the body, including the lungs, is different when a drug is administered over 30-90 minutes at a low rate, versus over a fraction of a minute at a high rate (*e.g.*, almost a bolus dose). In particular, a POSA would understand that at low rates of administration, the lungs may absorb all of the drug, and the pharmacokinetics (*e.g.*, blood levels) may never spike; rather, plasma levels of the drug are more likely to slowly rise to a steady state. With a bolus dose, or one inhaled in only 1 to 3 breaths, a POSA could expect a faster and higher spike in blood levels. And with inhalation administration, there could be spillover from the lungs (site of absorption by the body) into systemic circulation; such spillover would be much less likely with a slower rate of administration (for example, from a lengthier continuous nebulization). The

- Effects: bolus dosing ≠ long duration dosing
- Spillover affects drug impact to patient

Source: EX2052, ¶51.

JESC Demonstrates Non-Linearity

218 **Inhaled treprostinil is a potent pulmonary vasodilator in severe pulmonary hypertension**

R. Voswinckel, M.G. Kohstall, B. Enke, T. Gessler, F. Reichenberger, H.A. Ghofrani, W. Seeger, H. Olschewski. *Medical Clinic 2, Department of Internal Medicine, Giessen, Germany*

Background: Treprostinil has been approved for therapy of PAH (US and Canada) as continuous subcutaneous infusion. However, local pain at the infusion site is a major drawback. Inhaled therapy with another stable prostacyclin analogue (iloprost) has been approved for PPH (EMEA). In this study we investigated the acute hemodynamic response to inhaled treprostinil.

Methods: Open-label, single blind placebo-controlled clinical study. After placement of a Swan-Ganz catheter and a femoral artery line, patients inhaled solvent solution (placebo) (n=8) or treprostinil for 6 min (OptiNeb ultrasound nebulizer, Nebu-tec, Germany) in concentrations of 16, 32, 48, and 64 µg/ml (n=6, 6, 6, and 3 patients). Measurement was performed before and after 0, 15, 30, 60, 90, 120, 150 and 180 min. The mean area between the placebo and the treprostinil curves (ABC186) was calculated (baseline=100%).

Results: We investigated idiopathic PAH (n=10), collagen vascular disease (n=5), chronic thromboembolic disease (n=9), and pulmonary fibrosis (n=5), f/m = 19/10, age 56 ± 3 years, PAP, PAWP, and CVP 51.3 ± 2.2, 9.2 ± 0.8, and 6.6 ± 0.6 mmHg, CO 4.4 ± 0.3 l/min, SvO2 62.3 ± 1.2%, PVR 885 ± 72 dyn s cm^{-5}. At 16µg/ml there were no significant adverse events. Headache, cough or bronchoconstriction were observed in 2, 1, and 2 patients at 32, 48, and 64 µg/ml. These were mild and transient in all patients but one (64 µg/ml) who complained of major headache for 1 hour. Placebo inhalation was followed by slowly increasing PVR. Compared to this, the maximum treprostinil effect was reached after about 50 min and half-maximal effects at about 110 min. The ABC186 for PVR was –24.7 ± 4.4, -28.7 ± 4.9, and –29.0 ± 4.7%; PAP –14.4 ± 3.3, -13.5 ± 5.2, -13.1 ± 2.6%; SAP –5.1 ± 3.0, -6.0 ± 3.1, -3.8 ± 2.1% at 16, 32 and 48 µg/ml.

Conclusion: Treprostinil inhalation results in a significant long-lasting pulmonary vasodilatation. With the applied technology, at a concentration of 16µg/ml, near maximal pulmonary vasodilatation is achieved without adverse effects. At higher doses, local and systemic side effects may occur, whereas pulmonary selectivity is preserved.

This study was supported by Lung Rx.

- At 16 µg/mL, JESC described "maximum treprostinil effect" after about 50 minutes
- Near maximal vasodilation, without adverse effects, at 16 µg/mL
- Data shows increasing concentration does not necessarily increase benefit to patient

Sources: Paper No. 29, 20-21; EX1007; EX2052, ¶¶ 65-67.

Guesswork ≠ Reasonable Expectation of Success

testimony—supports the Board's finding that optimizing the four interdependent lipid components in the prior art nucleic acid-lipid particles would not have been routine, and Moderna's proposed adjustments to the various lipid components are hindsight driven. *See id.* The unpredictable interactivity between the various lipid components renders the claims of the '069 nonobvious. *See Applied Materials*, 692 F.3d at 1298.

CONCLUSION

We have considered Moderna's remaining arguments but we find them unpersuasive. Accordingly, the decision of the Board is affirmed.

AFFIRMED

TEVA PHARMACEUTICALS USA, INC., Appellant

v.

CORCEPT THERAPEUTICS, INC., Appellee

2021-1360

United States Court of Appeals, Federal Circuit.

Decided: December 7, 2021

Background: Challenger filed petition for post-grant review of patent for method of treating certain cancers by concomitant administration of a glucocorticoid receptor antagonist (GRA) and steroidogenesis or CYP3A inhibitors. The Patent Trial and Appeal Board (PTAB), Cotta, Administrative Patent Judge, ruled that claims were not unpatentable as obvious. Challenger appealed.

Holdings: The Court of Appeals, Moore, Chief Judge, held that claims were not unpatentable as obvious.

Affirmed.

1. Patents ⇐1970(7)

The presence or absence of a reasonable expectation of success in obviousness determination is a question of fact, which the Court of Appeals reviews for substantial evidence. 35 U.S.C.A. § 103.

2. Patents ⇐1970(7)

Whether the Patent Trial and Appeal Board applied the correct standard in assessing reasonable expectation of success in obviousness determination is a question of law that the Court of Appeals reviews de novo. 35 U.S.C.A. § 103.

3. Patents ⇐768

Patent Trial and Appeal Board (PTAB) did not err by requiring challenger, seeking post-grant review of patent for method of treating certain cancers by concomitant administration of a glucocorticoid receptor antagonist (GRA) and steroidogenesis or CYP3A inhibitors, to show a reasonable expectation of success for a specific mifepristone dosage, because patent claim required safe administration of a specific amount of mifepristone, namely, 600 mg per day. 35 U.S.C.A. § 103.

4. Patents ⇐687

The reasonable-expectation-of-success analysis in obviousness determination must

[3–5] The Board did not err by requiring Teva to show a reasonable expectation of success for a specific mifepristone dosage. The reasonable-expectation-of-success analysis must be tied to the scope of the claimed invention. *See Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 966 (Fed. Cir. 2014) ("[F]ailure to consider the appropriate scope of the . . . claimed invention in evaluating the reasonable expectation of success . . . constitutes a legal error . . . ."); *see also Intelligent Bio-Sys., Inc.*, 821 F.3d at 1367. Here, claim 1 of the '214 patent requires safe administration of a specific amount of mifepristone, 600 mg per day. *See Final Decision* at *7–9 (construing claims to require safe administration, rather than just administration).

Thus, the Board was required to frame its reasonable-expectation-of-success analysis around that specific dosage of mifepristone. To be clear, this does not mean Teva was required to prove a skilled artisan would have precisely predicted safe co-administration of 600 mg of mifepristone. Absolute predictability is not required. *See, e.g., Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). But Teva was required to prove a reasonable expectation of success in achieving the specific invention claimed, a 600 mg dosage.

Source: Paper No. 55, 21 (citing *Teva Pharms. USA, Inc. v. Corcept Therapeutics, Inc.*, 18 F. 4th. 1377, 1381 (Fed. Cir. 2021).

No Reasonable Expectation Of Success For 15-90 µg Dose

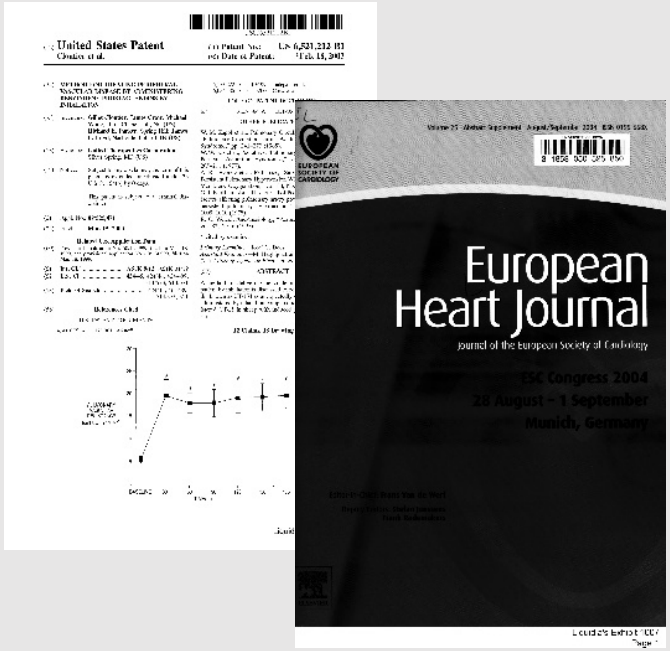
- Liquidia has not established any one dose allegedly disclosed in JESC
- No reasonable expectation of success from JESC because:
  - No known dose
  - Uncertainty of any estimations
- No reasonable expectation of success using 10-50% conversion factor
- Spillover and non-linearity negate expectation of success

Sources: Paper No. 29, 20-21, 23-24; Paper No. 55, 11-18, 20-21; EX2052, ¶51.

Ground 2

Ground 2 Fails For Same Reasons As Ground 1

Ground 2: '212 Patent + JESC



- JESC not proven to be prior art
- No teaching of claimed dose
- Dr. Hill: Liquidia's references do not teach "therapeutically effective" limitation
- No reasonable expectation of success

Sources: Paper No. 29, 40-44; Paper No. 55, 22-25; EX1006; EX1007.

Unknown Doses Do Not Alleviate Side Effect Concerns

JESC

- Inhaled concentrations over 6 minutes (unknown dose)
- Any side effect teachings inapplicable to different concentrations over 1-3 breaths

Sources: Paper No 29, 40-44; Paper No. 55, 20-21, 23; EX1007.

Liquidia's References Do Not Teach Reducing Breaths For Treprostinil

Bolus Inhalation of rhDNase with the AERx System in Subjects with Cystic Fibrosis

Aerosolised prostacyclin in adult respiratory distress syndrome

LONG-TERM TREATMENT OF PRIMARY PULMONARY HYPERTENSION WITH AEROSOLIZED ILOPROST, A PROSTACYCLIN ANALOGUE

- Geller: rhDNase for cystic fibrosis patients
- Walmrath: reduces dose of prostacyclin to avoid spillover
- Hoeper: increasing iloprost dose, sometimes with more administrations per day

Sources: EX1034 (Geller); EX1048 (Walmrath); EX1047 (Hoeper); Paper No. 55 at 24; EX2053, ¶¶85-86.

Ground 2 Does Not Render The Asserted Claims Obvious

- Missing the claimed dose
- No disclosure of 1-3 breaths
- Liquidia's generic "optimization" and "titration" references do not teach reduction of breaths for administration of treprostinil

Sources: Paper No. 55, 23-25; EX2053, ¶¶85-86.

Secondary Considerations Show Nonobviousness

Tyvaso® Embodies Claim 1

'793 Patent, Claim 1	
1. A method of treating pulmonary hypertension comprising	✓
administering by inhalation to a human suffering from pulmonary hypertension	✓
a therapeutically effective single event dose	✓
of a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof	✓
with an inhalation device,	✓
wherein the therapeutically effective single event dose comprises from	✓
15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof	✓
delivered in 1 to 3 breaths.	✓

TYVASO (treprostinil) inhalation solution
Initial U.S. Approval: 2002
For Oral Inhalation Only

----------**INDICATIONS AND USAGE**----------

Tyvaso is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III symptoms, to increase walk distance. (1)

----------**DOSAGE AND ADMINISTRATION**----------

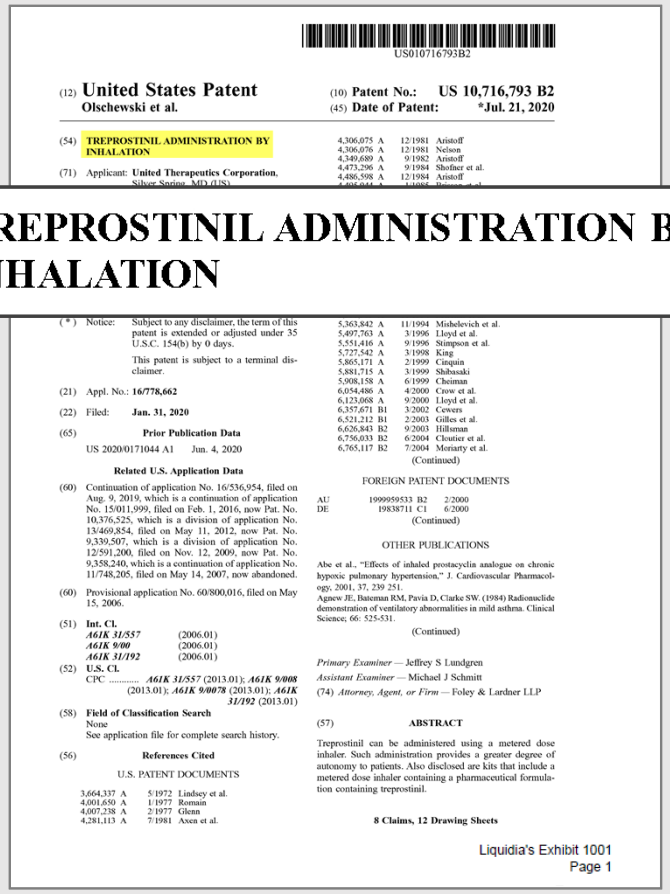
- Use only with the Tyvaso Inhalation System. (2.1)
- Administer undiluted, as supplied. A single breath of Tyvaso delivers approximately 6 mcg of treprostinil. (2.1)
- Administer in 4 separate treatment sessions each day approximately four hours apart, during waking hours. (2.1)
- Initial dosage: 3 breaths [18 mcg] per treatment session. If 3 breaths are not tolerated, reduce to 1 or 2 breaths. (2.1)
- Dosage should be increased by an additional 3 breaths at approximately 1-2 week intervals, if tolerated. (2.1)
- Titrate to target maintenance dosage of 9 breaths or 54 mcg per treatment session as tolerated. (2.1)

----------**DOSAGE FORMS AND STRENGTHS**----------

Sterile solution for oral inhalation: 2.9 mL ampule containing 1.74 mg treprostinil (0.6 mg per mL). (3)

Sources: Paper No. 29, 57; Paper No. 55, 25-26; EX1001, 25; EX2034, 1.

The Claimed Invention Produced a New and Unexpected Result



US010716793B2

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

(10) **Patent No.: US 10,716,793 B2**
(45) **Date of Patent: *Jul. 21, 2020**

(54) **TREPROSTINIL ADMINISTRATION BY INHALATION**

(71) Applicant: **United Therapeutics Corporation**, Silver Spring, MD (US)

TREPROSTINIL ADMINISTRATION BY INHALATION

(*) 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.: **16/778,662**

(22) Filed: **Jan. 31, 2020**

(65) **Prior Publication Data**

US 2020/0171044 A1 Jun. 4, 2020

Related U.S. Application Data

(60) Continuation of application No. 16/536,954, filed on Aug. 9, 2019, which is a continuation of application No. 15/011,999, filed on Feb. 1, 2016, now Pat. No. 10,376,525, which is a division of application No. 13/469,854, filed on May 11, 2012, now Pat. No. 9,339,507, which is a division of application No. 12/591,200, filed on Nov. 12, 2009, now Pat. No. 9,358,240, which is a continuation of application No. 11/748,205, filed on May 14, 2007, now abandoned.

(60) Provisional application No. 60/800,016, filed on May 15, 2006.

(51) **Int. Cl.**
A61K 31/557 (2006.01)
A61K 9/00 (2006.01)
A61K 31/192 (2006.01)

(52) **U.S. Cl.**
CPC ***A61K 31/557*** (2013.01); ***A61K 9/008*** (2013.01); ***A61K 9/0078*** (2013.01); ***A61K 31/192*** (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**

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5,497,763	A	3/1996	Lloyd et al.
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(Continued)

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(Continued)

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Abe et al., "Effects of inhaled prostacyclin analogue on chronic hypoxic pulmonary hypertension," J. Cardiovascular Pharmacology, 2001, 37, 239 251.
Agnew JE, Bateman RM, Pavia D, Clarke SW. (1984) Radionuclide demonstration of ventilatory abnormalities in mild asthma. Clinical Science; 66: 525-531.

(Continued)

Primary Examiner — Jeffrey S Lundgren
Assistant Examiner — Michael J Schmitt
(74) *Attorney, Agent, or Firm* — Foley & Lardner LLP

(57) **ABSTRACT**

Treprostinil can be administered using a metered dose inhaler. Such administration provides a greater degree of autonomy to patients. Also disclosed are kits that include a metered dose inhaler containing a pharmaceutical formulation containing treprostinil.

8 Claims, 12 Drawing Sheets

Liquidia's Exhibit 1001
Page 1

> Study iii) successfully demonstrated that the inhalation time could be reduced to literally one single breath of 2000 µg/ml treprostinil solution, thereby applying a dose of 15 µg. This drug administration with a single breath induced pulmonary vasodilation for longer than 3 hours compared to placebo inhalation. Side effects were minor, of low frequency and not related to drug concentration. It was a surprising finding that such high concentrations of treprostinil were so well tolerated.

EX1001 at 17:44-18:6.

> Conclusion:
> Inhaled treprostinil can be applied in high doses (up to 90 µg) with a minimal inhalation time. Inhaled treprostinil exerts high pulmonary selectivity and leads to a long-lasting pulmonary vasodilation.

EX1001 at 18:7-11.

Sources: Paper No. 29, 55-57; EX1001, 17:44-18:11.

Unexpected Results

- Prior art taught away from higher concentration and lower number of breaths, but claimed dosing produced unexpected results (Paper No. 29, 55-57)

- Especially unexpected that claimed dosing using fewer breaths led to longer duration of action compared to prior art since JESC implies lower concentration, longer time interval produced longer duration than JAHA

Sources: Paper No. 29, 55-57; Paper No. 55, 25-26.

More Secondary Considerations

Tyvaso Satisfies A Long-Felt But Unmet Need

Experts agree Tyvaso meets the needs of an underserved patient population

- EX2055, 31:11-16
- EX1108, 142:13-143:11

> "Dr. Steiner's [a practicing physician] testimony of longfelt need, moreover, supports the inference that it was difficult for researchers to create a therapeutically effective, extended-release product. Because a desire existed for such a product, researchers, presumably, would have created one if they were able to do so."

Paper No. 55, 26 (citing *In re Cyclobenzaprine Hydrochloride*, 676 F.3d 1063, 1083 (Fed. Cir. 2012).

Petitioner's Deliberate Copying of Tyvaso

Corporate filings, press releases, and publications

- Paper No. 29 (citing EX2084, EX2085, EX2036, EX2089)
- Paper No. 55, 26 (citing EX2061)

> "[C]opying by a competitor is a relevant consideration in the objective indicia analysis."

Paper No. 29, 57 (citing *Liqwd, Inc. v. L'Oreal USA, Inc.*, 941 F.3d 1133, 1137 (Fed. Cir. 2019).

Sources: Paper No. 29, 57; Paper No. 55, 26; EX1108; EX2055.

Petitioner's Reply Contains Improper Evidence

Petitioner's Reply Contains Evidence & Arguments That Exceed Permissible Scope

- It is "improper for a reply to present new evidence (including new expert testimony) that could have been presented in a prior filing." Trial Practice Guide, 74.
- Board denied Petitioner's Motion to submit Supplemental Information (Paper No. 30), but Petitioner exceeds permissible scope in its Reply using same evidence.
- PO identified numerous new exhibits and arguments relating to public accessibility—evidence that could have been presented with the Petition (Paper No. 47).

Sources: Paper No. 30; Paper No. 47.

Sur-Reply Responds to Petitioner's Reply & Necessitated By Belated Reply Evidence

- Paper No. 62 shows that the challenged exhibits and testimony tie directly to Petitioner's Reply.
- The challenged exhibits and testimony of PO Sur-Reply are also directed to the 2 aspects of Petitioner's Reply that exceed permissible scope – the belated (i) new evidence of public accessibility and (ii) new dosing calculations. (Paper No. 55, 11.)
- During discussion of PO's request to strike portions of Petitioner's Reply, Judge Kaiser noted that it "would be hard to understand the testimony without any ability to look at the [exhibit used to cross-examine Reply Declarant on Declaration topic]." (EX2104, 34-35.)

Source: Paper No. 55, 11; Paper No. 62; EX2104, 34-35.

Petitioner's Exhibits Should Be Excluded

- Petitioner's nebulization rate used in its dose calculations relies on evidence which should be excluded (Paper No. 66):
  - The label exhibits (1029, 1050, 1066, 1074, & 1078) should be excluded as failing to satisfy FRE 902 and *Celltrion, Inc. v. Biogen, Inc.*, IPR2016-01614, Paper No. 65 at 17-20 (PTAB Feb. 21, 2018)
  - EX1037 should be excluded as it does not satisfy multiple FRE requirements, which are not fixed by EX1086, EX1087
  - Navigation page for Nebutec shows 11 different Optineb guides (Paper No. 55, 14 citing EX1087, 9)

Sources: Paper No. 66, 2-10, 14-15; Paper No. 55, 14; EX1029; EX1050; EX1066; EX1074; EX1078; EX1086; EX1087, 9.

EX1037: Optineb Manual Should Be Excluded

- EX1037 purports to show a "2005" manual which allegedly disclosed an output rate of 0.6 ml/min (EX1037, 28)
- Following objection, Liquidia served EX1086 and EX1087, neither of which contain a German version from 2005 that could have been the basis of the translation provided in EX1037
- Clearly they are DIFFERENT documents:
  - Liquidia asserts EX1086 and exhibit E of EX1087 are both from 2004
  - EX1086 and exhibit E of EX1087 both disclose output rate of "<0.6 ml/min" (see p. 28 referencing original page numbering of both exhibits)

Source: Paper No. 66, 2-10.

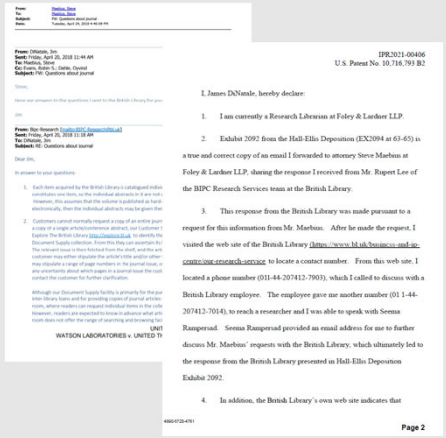
Petitioner's Label Exhibits Should Be Excluded

- EX1029, 1050, 1066, 1074, and 1078 are not authenticated
- No source information provided for any of these exhibits except EX1029
- As to EX1029, Petitioner belatedly attempts to provide new evidence of its source in its Opposition, long after the period for filing supplemental evidence expired (Paper No. 68, 11, n.3-4)
- Petitioner's citations to depositions of experts offer no information about the source of the specific labels in these exhibits
- The fact that the experts prescribe or use the products on patients has no bearing on whether a specific version of that product's label existed and had an identifiable source to allow for authentication

Source: Paper No. 66, 2-4.

UTC's Exhibits Should Not Be Excluded

Patent Owner's Exhibits Should Not Be Excluded



IPR2021-00406
U.S. Patent No. 10,716,793 B2

I, James DiNatale, hereby declare:

1. I am currently a Research Librarian at Foley & Lardner LLP.

2. Exhibit 2092 from the Hall-Ellis Deposition (EX2094 at 63-65) is a true and correct copy of an email I forwarded to attorney Steve Maebius at Foley & Lardner LLP, sharing the response I received from Mr. Rupert Lee of the BIPC Research Services team at the British Library.

3. This response from the British Library was made pursuant to a request for this information from Mr. Maebius. After he made the request, I visited the web site of the British Library (https://www.bl.uk/business-and-ip-centre/our-research-service to locate a contact number. From this web site, I located a phone number (011-44-207412-7903), which I called to discuss with a British Library employee. The employee gave me another number (01 1-44-207412-7014), to reach a researcher and I was able to speak with Seema Rampersad. Seema Rampersad provided an email address for me to further discuss Mr. Maebius' requests with the British Library, which ultimately led to the response from the British Library presented in Hall-Ellis Deposition Exhibit 2092.

4. In addition, the British Library's own web site indicates that

Page 2

DECLARATION OF NATHANIEL E FRANK-WHITE

1. I am a Records Request Processor at the Internet Archive. I make this declaration of my own personal knowledge.

2. The Internet Archive is a website that provides access to a digital library of Internet sites and other cultural artifacts in digital form. Like a paper library, we provide free access to researchers, historians, scholars, and the general public. The Internet Archive has partnered with and receives support from various institutions, including the Library of Congress.

3. The Internet Archive has created a service known as the Wayback Machine. The Wayback Machine makes it possible to browse more than 450 billion pages stored in the Internet Archive's web archive. Visitors to the Wayback Machine can search archives by URL (i.e., a website address). If archived records for a URL are available, the visitor will be presented with a display of available dates. The visitor may select one of those dates, and begin browsing an archived version of the Web. Links on archived files in the Wayback Machine point to other archived files (whether HTML pages or other file types), if any are found for the URL indicated by a given link. For instance, the Wayback Machine is designed such that when a visitor clicks on a hyperlink on an archived page that points to another URL, the visitor will be served the archived file found for the hyperlink's URL with the closest available date to the initial file containing the hyperlink.

4. The archived data made viewable and browseable by the Wayback Machine is obtained by use of web archiving software that automatically stores copies of files available via the Internet, each file preserved as it existed at a particular point in time.

5. The Internet Archive assigns a URL on its site to the archived files in the format http://web.archive.org/web/[Year as yyyy][Month as mm][Day as dd][Time code as hh:mm:ss][Archived URL] aka an "extended URL". Thus, the extended URL http://web.archive.org/web/19970126043828/http://www.archive.org/ would be the URL for the record of the Internet Archive home page HTML file (http://www.archive.org/) archived on January 26, 1997 at 4:38 a.m. and 28 seconds (1997/01/26 at 04:38:28). The date indicated by an extended URL applies to a preserved instance of a file for a given URL, but not necessarily to any other files linked therein. Thus, in the case of a page constituted by a primary HTML file and other separate files (e.g., files with images, audio, multimedia, design elements, or other embedded content) linked within that primary HTML file, the primary HTML file and the other files will each have their own respective extended URLs and may not have been archived on the same dates.

IPR2021-00406
United Therapeutics EX2106

Deposition Ex. 2092 attached to EX2094 (British Library Email)

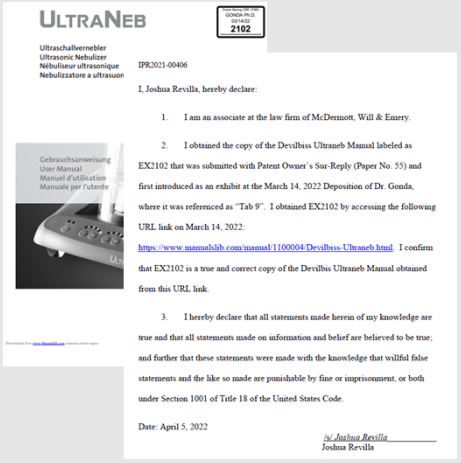
- Complete
- Authenticated by EX2105 (DiNatale Decl.)
- Undermines Liquidia's assertions regarding availability

EX2100-EX2102 (Schill instructions for use)

- Authenticated by EX2106
- Used at Gonda deposition
- Undermine Liquidia's assertions regarding rates and efficiencies

Sources: Paper No. 69, 2-7, 9-11; Dep. Ex. 2092; EX2094; EX2100; EX2101; EX2099, 164:1-176:5.

Patent Owner's Exhibits Should Not Be Excluded


ULTRANEB

Ultraschallvernebler
Ultrasonic Nebulizer
Nébuliseur ultrasonique
Nebulizzatore a ultrasuon

GONDA Ph.D.
03/14/22
2102

Gebrauchsanweisung
User Manual
Manuel d'utilisation
Manuale per l'utente

IPR2021-00406

I, Joshua Revilla, hereby declare:

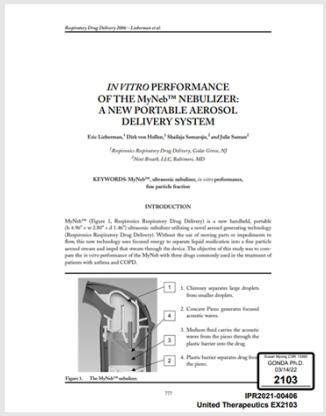
1. I am an associate at the law firm of McDermott, Will & Emery.

2. I obtained the copy of the Devilbiss Ultraneb Manual labeled as EX2102 that was submitted with Patent Owner's Sur-Reply (Paper No. 55) and first introduced as an exhibit at the March 14, 2022 Deposition of Dr. Gonda, where it was referenced as "Tab 9". I obtained EX2102 by accessing the following URL link on March 14, 2022: https://www.manualslib.com/manual/1100004/Devilbiss-Ultraneb.html. I confirm that EX2102 is a true and correct copy of the Devilbis Ultraneb Manual obtained from this URL link.

3. I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code.

Date: April 5, 2022

/s/ Joshua Revilla
Joshua Revilla


IN VITRO PERFORMANCE OF THE MyNeb™ NEBULIZER: A NEW PORTABLE AEROSOL DELIVERY SYSTEM

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KEYWORDS: MyNeb™, ultrasonic nebulizer, in vitro performance, fine particle fraction

INTRODUCTION

1. Chimney separates large droplets from smaller droplets.
2. Concave Piezo generates focused acoustic waves.
3. Medium fluid carries the acoustic waves from the piezo through the plastic barrier into the drug.
4. Plastic barrier separates drug from the piezo.

Figure 1. The MyNeb™ nebulizer.

GONDA Ph.D.
03/14/22
2103

IPR2021-00406
United Therapeutics EX2103

Deposition Ex. 2102 (DeVilbiss Manual)

- Authenticated by EX2107 (Revilla Decl.)
- Used at Gonda deposition
- Undermines Liquidia's assertions regarding rates and efficiencies

EX2103 (Lieberman)

- Only dispute appears to be availability before May 15, 2006 (Paper 65, 7-8); EX2103 is evidence of general knowledge of POSA
- Used at Gonda deposition
- Undermines Liquidia's assertions regarding rates and efficiencies

Source: Paper No. 69, 12-15; EX2102; EX2107; EX2103; EX2099, 180:22-185:7, 198:9-201:6.