No. S283862

IN THE SUPREME COURT
OF THE STATE OF CALIFORNIA

GILEAD SCIENCES, INC.,
Petitioner,
v.
SUPERIOR COURT OF THE STATE OF CALIFORNIA, COUNTY OF SAN FRANCISCO,
Respondent,
and
GILEAD TENOFOVIR CASES,
Real Parties in Interest.

Review of a decision from the Court of Appeal, First Appellate District, Division Four, No. A165558
San Francisco County Superior Court No. CJC-19-005043
Hon. Andrew Y.S. Cheng

APPLICATION BY PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA, BIOTECHNOLOGY INNOVATION ORGANIZATION, AND CALIFORNIA LIFE SCIENCES TO FILE AN *AMICUS CURIAE* BRIEF IN SUPPORT OF PETITIONER

*Ashley M. Simonsen (Bar No. 275203)
Alice L. Phillips (Bar No. 322070)
COVINGTON & BURLING LLP
1999 Avenue of the Stars
Los Angeles, CA 90067
Telephone: (424) 332-4782
Facsimile: (424) 332-4749
asimonsen@cov.com

Michael X. Imbroscio
COVINGTON & BURLING LLP
850 Tenth Street NW
Washington, DC 20001

Gregory L. Halperin
COVINGTON & BURLING LLP
620 Eighth Avenue
New York, NY 10018

Attorneys for Amici Curiae Pharmaceutical Research and Manufacturers of America, Biotechnology Innovation Organization, and California Life Sciences.

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Pursuant to Appellate Rule 8.200(c), the Pharmaceutical Research and Manufacturers of America ("PhRMA"), Biotechnology Innovation Association ("BIO"), and California Life Sciences ("CLS") respectfully seek leave to file the accompanying amicus curiae brief in support of Gilead Sciences, Inc.[1]

PhRMA represents the country's leading innovative biopharmaceutical research companies, which are laser focused on developing innovative medicines that transform lives and create a healthier world. PhRMA advocates for solutions to ensure patients can access and afford medicines that prevent, treat and cure disease. Over the last decade, PhRMA member companies have invested more than $800 billion in the search for new treatments and cures, and they support nearly 5 million jobs in the United States.[2]

BIO is the principal trade organization representing the biotechnology industry domestically and abroad. BIO has more than 1,000 members, which span the for-profit and nonprofit sectors and range from small start-up companies and biotechnology centers to research universities and Fortune 500 companies. BIO's members devote billions of dollars annually to researching and developing biotechnological healthcare, agricultural, environmental, and industrial products that cure diseases,

[1] Pursuant to Rule 8.200(c), PhRMA, BIO, and CLS certify that no party or party's counsel authored this brief in whole or in part. No party or party's counsel made a monetary contribution intended to fund the preparation or submission of this brief, and no person or entity other than *amici curiae*, their members, or their counsel made such a monetary contribution. Although Gilead Sciences, Inc. is a member of PhRMA, BIO, and CLS, it has not contributed financially to the preparation of this brief.

[2] *2024 PhRMA Annual Membership Survey* (2024) p. 3 tbl. 1 <https://phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Refresh/Report-PDFs/PhRMA_2024-Annual-Membership-Survey.pdf>.

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improve food security, create alternative energy sources, and deliver many other benefits.

CLS is an influential life-sciences member organization, advocating for the sector and its diverse innovation pipeline. For more than 30 years, CLS has served the community by supporting companies of all sizes, from early-stage innovators to established industry leaders in the fields of biotechnology, pharmaceuticals, medical devices, and diagnostics. CLS also works closely with universities, academic and research institutions, service providers, the investment community, and other partners – all of whom are integral components of a healthy, collaborative innovation ecosystem. CLS members consist of scientists, innovators, entrepreneurs, and leaders that have made California the largest, most innovative, and most productive life-sciences ecosystem in the world. From four different offices throughout California (and one in the District of Columbia), CLS works to shape public policy, improve access to breakthrough technologies, educate lawmakers, advance equity within the life-sciences ecosystem, and grow California's life-sciences economy by championing innovative solutions to some of our most pressing challenges. CLS's mission is to protect and nurture California's life-sciences industry, empowering discoveries that lead to healthier lives around the world.

This case is of critical importance to the members of PhRMA, BIO, and CLS, who must make daily scientific and strategic decisions on how to pursue regulatory approval of their products in the face of scientific uncertainty and increasingly massive and costly litigation. PhRMA, BIO, and CLS hope to assist the Court in resolving this case by providing background on the discovery, development, and regulatory approval of medicines in the United States.

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Respectfully submitted,

/s/ Ashley M. Simonsen

Ashley M. Simonsen
Alice L. Phillips
COVINGTON & BURLING LLP
1999 Avenue of the Stars
Los Angeles, CA 90067
Telephone: (424) 332-4782
Facsimile: (424) 332-4749
asimonsen@cov.com
aphillips@cov.com

Michael X. Imbroscio
COVINGTON & BURLING LLP
850 Tenth Street NW
Washington, DC 20001
Telephone: (202) 662-5694
Facsimile: (202) 778-5694
mimbroscio@cov.com

Gregory L. Halperin
COVINGTON & BURLING LLP
620 Eighth Avenue
New York, NY 10018
Telephone: (212) 841-1166
Facsimile: (646) 441-9166
ghalperin@cov.com

Counsel for Amici Curiae Pharmaceutical Research and Manufacturers of America, Biotechnology Innovation Organization, and California Life Sciences

Dated: November 4, 2024

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PROOF OF SERVICE

I am a resident of Washington, D.C. and over the age of eighteen years, and not a party to the within action. My business address is 850 Tenth Street NW, Washington D.C. 20001. On November 4, 2024, I served the following document(s) described as:

APPLICATION BY PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA, BIOTECHNOLOGY INNOVATION ORGANIZATION, AND CALIFORNIA LIFE SCIENCES TO FILE AN *AMICUS CURIAE* BRIEF IN SUPPORT OF PETITIONER

on the interested parties in this action as follows:

GRANT & EISENHOFFER P.A.
M. Elizabeth Graham
2325 Third Street, Suite 329
San Francisco, California 94107
Telephone: (415) 229-9720
Email: egraham@gelaw.com

JENNER LAW, P.C.
Robert K. Jenner
3600 Clipper Mill Road, Suite 240
Baltimore, Maryland 21211
Telephone: (410) 413-2155
Email: rjenner@jennerlawfirm.com

MOSKOVITZ APPELLATE TEAM
Myron Moskovitz
90 Crocker Avenue
Oakland, California 94611
Telephone: (510) 384-0354
Email: myronmoskovitz@gmail.com

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KERSHAW, COOK & TALLEY, P.C.
William A. Kershaw
401 Watt Avenue, Suite 1
Sacramento, California 95864
Telephone: (916) 779-7000
Email: bill@kctlegal.com

SCHNEIDER WALLACE COTTRELL KONECKY LLP
Amy Eskin
2000 Powell Street, Suite 1400
Emeryville, California 94608
Telephone: (510) 740-2936
Email: aeskin@schneiderwallace.com

ESNER, CHANG & BOYER
Andrew N. Chang, SBN 84544
Holly N. Boyer, SBN 221788
234 East Colorado Boulevard, Suite 975
Pasadena, California 91101
Telephone: (626) 535-9860
Email: achang@ecbappeal.com
hboyer@ecbappeal.com

THE LAWRENCE LAW FIRM
Jeffrey Lawrence
Levi's Plaza
1160 Battery Street East, Suite 100
San Francisco, CA 94111
(415) 685-5030
jeffreyl@jlawrencelaw.com

BURG SIMPSON ELDREDGE HERSH & JARDINE, P.C.
Seth A. Katz
40 Inverness Drive East
Englewood, CO 80112
(303) 792-5595
skatz@burgsimpson.com

Document received by the CA Supreme Court.

WASHINGTON LEGAL FOUNDATION
2009 Massachusetts Avenue,
NW Washington, DC 20036
Cory L. Andrew
John M. Masslon II
(202) 588-0302
candrews@wlf.org

INTERNATIONAL CENTER FOR LAW
& ECONOMICS
Geoffrey A. Manne
Kristen Stout
Jeremy Kidd
1104 NW 15th Avenue, Suite 300
Portland, OR 97209
(503) 770-0076
kstout@laweconcenter.org

QUINN EMANUEL URQUHART
& SULLIVAN, LLP
John M. Potter, Esq.
50 California Street, 22nd Floor
San Francisco, CA 94111
(415) 875-6600 johnpotter@quinnemanuel.com

WILMER CUTLER PICKERING
HALE AND DORR LLP
Joseph Meyer
Thomas G. Saunders
Gary M. Fox
2100 Pennsylvania Ave.,
NW Washington, DC 20037
(202) 663-6000
joseph.meyer@wilmerhale.com
thomas.saunders@wilmerhale.com
gary.fox@wilmerhale.com

BOWMAN AND BROOKE LLP
Paul A. Alarcon, Esq.
600 Anton Boulevard, Suite 650
Costa Mesa, CA 92626
Telephone: (310) 380-6500
paul.alarcon@bowmanandbrooke.com

Document received by the CA Supreme Court.

O'MELVENY & MYERS LLP
Charles C. Lifland, Esq.
Sabrina H. Strong, Esq.
Jeffrey L. Fisher, Esq.
Jason Zarrow, Esq.
400 South Hope Street
18th Floor
Los Angeles, CA 90071
(213) 430-6000
clifland@omm.com

GUTIERREZ PRECIADO HOUSE
Calvin R. House, Esq.
3020 East Colorado Boulevard
Pasadena, CA 91107
(626) 449-2300
calvin.house@gphlawyers.com

GIBSON, DUNN & CRUTCHER LLP
Theane Evangelis, Esq.
Daniel Adler, Esq.
333 South Grand Avenue
Los Angeles, CA 90071
(213) 229-7000
dadler@gibsondunn.com

GHOST AUTONOMY INC.
Seth Travis
900 Villa Street
Mountain View, CA 94041
sethatravis@gmail.com

ATLANTIC LEGAL FOUNDATION
Lawrence S. Ebner
1701 Pennsylvania Ave.
Suite 200
Washington, D.C. 20006
(202) 349-1421
Lawrence.ebner@atlanticlegal.org

Document received by the CA Supreme Court.

PAUL, WEISS, RIFKIND, WHARTON &
GARRISON LLP
Randy Luskey
Kannon K. Shanmugam
535 Mission Street, 24th floor
San Francisco, CA 94105
(628) 432-5112
rluskey@paulweiss.com

ORRICK, HERRINGTON & SUTCLIFFE LLP
E. Joshua Rosenkranz
Andrew Silverman
Elizabeth Bixby
51 West 52nd Street
New York, NY 10015
Telephone: (212) 506-5000
Facsimile: (212) 506-5151
jrosenkranz@orrick.com
asilverman@orrick.com
ebixby@orrick.com

[x] (BY TRUEFILING) By filing and serving the foregoing through Truefiling such that the document will be sent electronically to the eservice list on November 4, 2024;

I declare under penalty of perjury under the laws of the State of California that the foregoing is true and correct and that this proof of service is executed at Washington, D.C. on November 4, 2024.

/s/ Anand Balaji
Anand Balaji

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*Ashley M. Simonsen (Bar No. 275203)
Alice L. Phillips (Bar No. 322070)
COVINGTON & BURLING LLP
1999 Avenue of the Stars
Los Angeles, CA 90067
Telephone: (424) 332-4782
Facsimile: (424) 332-4749
asimonsen@cov.com

Michael X. Imbroscio
COVINGTON & BURLING LLP
850 Tenth Street NW
Washington, DC 20001

Gregory L. Halperin
COVINGTON & BURLING LLP
620 Eighth Avenue
New York, NY 10018

Attorneys for Amici Curiae Pharmaceutical Research and Manufacturers of America, Biotechnology Innovation Organization, and California Life Sciences.

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CERTIFICATE OF INTERESTED ENTITIES OR PERSONS

Pursuant to Appellate Rule 8.208, Pharmaceutical Research and Manufacturers of America ("PhRMA"), Biotechnology Innovation Organization("BIO"), and California Life Sciences ("CLS") state that they are trade associations with no parent corporations. No entity or person has a 10% or greater ownership interest in PhRMA, BIO, or CLS. PHRMA, BIO, and CLS do not know of any person or entity, other than the parties themselves, that has a financial or other interest in the outcome of the proceeding that the Justices should consider in determining whether to disqualify themselves. A list of PhRMA's member companies can be found at http://www.phrma.org/about. A list of BIO's members is available at https://www.bio.org/bio-member-directors. A list of CLS's members can be found at https://www.califesciences.org/member-directory.

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INTRODUCTION

Discovering, developing, and delivering innovative life-saving treatments is a complicated, expensive, and uncertain enterprise. The vast majority of potential medicines that reach human studies fail to make it to market, either because it turns out that somewhere along the development path the medicine shows a lack of necessary effectiveness or because it presents unacceptable safety risks. To ensure constant and steady innovation, companies must devote extensive resources across a range of potential drug candidates and are often required to make crucial resource allocation decisions with only preliminary information about whether a product might ultimately be effective to treat a certain condition and whether its benefits may outweigh its risks.

The Food and Drug Administration ("FDA") intensely regulates the entire drug development process, including by establishing an exacting testing regime where medicines are rigorously tested first in the laboratory and thereafter in closely monitored evolving "phases" of clinical (human) trials. At the early stages of clinical testing, the trials conducted are short in duration, narrow in scope, and small in size. The goal of these early studies is to identify threshold safety or tolerability issues and understand the activity of the drug in the human body. These studies lay the groundwork for further studies that begin to evaluate whether the drug will actually provide some clinical benefit, including potential dosing. These initial studies, by design, are not intended to answer the ultimate question in drug development: whether there is substantial evidence that the benefits of the medicine outweigh the treatment's risks such that the medicine can obtain regulatory approval.

In this sense, the entire basis of the Court of Appeal's decision here rests on a faulty premise. In no world and under no circumstances could a company "know" that a medicine like TAF – still in this early and limited

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development stage – will prove out to be equally effective as or have a better safety profile than a marketed product like TDF that has gone through the entire development process, and there is no reasonable permissible basis upon which a jury could so conclude. To assign potential tort liability based on decisions so early in the drug development process is to fundamentally misunderstand the goals and limitations of the different stages in the clinical development process, particularly when comparing treatments against each other. Ultimately, the Court of Appeal's foreseeability and culpability analyses rested on untenable inferences fundamentally incompatible with modern drug development that will impose huge and unwarranted litigation costs on biopharmaceutical companies.

Nor is there any need to use the tort system to align appropriate incentive structures for the industry. Companies already have keen incentives to bring new and better medicines to market after thorough study, and the negligence framework endorsed by the Court of Appeal has the real potential to actually deter both biopharma investment at the front end and incremental product improvement at the back end. This brief seeks to help inform the Court's understanding of the drug development and approval process, including the realities and key dynamics of the biopharmaceutical market. The brief proceeds in two parts.

First is an overview of the drug development process, including the challenges in getting medicines to market and the goals and limitations of clinical testing. The FDA imposes strict "preclinical" requirements before prospective compounds can even be tested in human "clinical" trials. Once a drug candidate is allowed to proceed into the clinic, Phase I and Phase II clinical trials provide important but decidedly preliminary information regarding the activity, safety, tolerability, and potential efficacy of a new medicine. Generally, if the Phase I and Phase II results are positive, Phase

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III clinical trials are then performed with larger patient populations, often in the hundreds or thousands of participants, carried out typically over the course of several years. Even for compounds that had shown promise in the early phases of clinical testing, approximately half will often nevertheless fail to satisfy the rigors of this Phase III testing, which is exactly why it is very common for companies to develop a range of compounds in a given therapeutic area to hedge against this considerable failure risk.

Crucially, results of Phase III trials are central to inform conclusions regarding the safety and efficacy of a potential medicine. Here, with only the preliminary 30-patient Phase I/II trial that Gilead conducted on TAF in 2003, it would have been impossible for Gilead to sufficiently understand the scope of potential safety issues with TAF such that it could have made some comparative judgment with TDF – the comparative judgment that the Court of Appeal's decision says should be the basis of substantial tort liability. Indeed, even had TAF successfully completed Phase III trials at that time, making the sort of definitive risk/benefit comparisons to TDF needed for a "knowledge"-based claim would have been equally unfeasible.

Second is an analysis of the realities of the drug development process missing from the Court of Appeal's decision. The biopharmaceutical market is highly competitive and already incentivizes companies to bring safe and innovative next generation medicines to patients with unmet needs in order to capture the first mover advantage. By contrast, the liability regime Plaintiffs advocate would disincentivize advances in medicines that are critical to promoting patient wellbeing. There is a litany of historical examples of groundbreaking next-generation innovations of existing FDA-approved medicines, and the Court of Appeal's foreseeability analysis rests on fundamental misconceptions of the drug development and approval processes and the FDA's comprehensive

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oversight. Imposing liability on a company for selling an FDA-approved, admittedly non-defective medicine because of some subsequent medical advance creates an untenable and ultimately unworkable liability regime.

DISCUSSION

The biopharmaceutical industry plays a critical role in delivering new, safe, and effective medicines that extend and improve the lives of patients. The drug development process is expensive, and PhRMA, BIO, and CLS members spend billions of dollars annually on research and development. On average, developing a new medicine and obtaining FDA approval takes ten to fifteen years and costs $2.6 billion.[3] Because so few drug candidates will ultimately progress to FDA approval, pharmaceutical companies often develop related or next-generation compounds to hedge against the very substantial failure risk. In turn, companies must make complicated decisions on where to allocate limited resources and choosing which drug candidates to prioritize in this process and commit investment resources is, at its heart, an unavoidably fraught exercise. Companies must make these resource allocation decisions based on decidedly imperfect information in determining which drug candidates should proceed through a clinical trial program. The Court of Appeal's decision presents companies with an impossible choice.

I. The Drug Development and Approval Process is Thorough, Costly, and Risk-Laden.

As the U.S. Supreme Court has recognized, bringing a new medicine to market is an "onerous and lengthy" process. (*Mutual Pharm Co., Inc. v.*

[3] PhRMA, *Biopharmaceuticals in Perspective: Fall 2020* (2020) p. 27 <https://www.phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/A-C/ChartPack_Biopharmaceuticals_in_Perspective_Fall2020.pdf> (hereafter *Biopharmaceuticals in Perspective*); *see also* DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs* (2016) 47 J. Health Econ. 20.

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Bartlett (2013) 570 U.S. 472, 476.) The complexities of developing a new, innovative medicine are driven by the stringent standards imposed by the FDA to gather the data necessary to assess the safety and efficacy of a new treatment. As the agency responsible for "protecting the public health by ensuring the safety" of medicines and "helping the public get the accurate, science-based information they need to use medical products,"[4] FDA closely examines extensive scientific and clinical data about a medicine as part of the approval process. (*See* 73 Fed. Reg. 49,603, 49,604 (Aug. 22, 2008) (FDA "makes approval decisions . . . based on a comprehensive scientific evaluation of the product's risks and benefits").) Indeed, FDA typically reviews and analyzes more than 100,000 pages of preclinical and clinical testing results as part of its approval process.[5] Those 100,000 pages of data are the result of extensive research, study, and analysis conducted before a medicine is submitted to FDA for approval. FDA will approve that new medicine only if it determines that the anticipated benefits "outweigh their known risks" for the intended patient population.[6]

A. The Goals of Early-Stage Preclinical and Clinical Testing are Focused and Limited.

Before studying a new medicine in humans, a biopharmaceutical company generally must conduct a series of laboratory and other preclinical studies to test how the medicine works and assess its safety. (21 C.F.R. § 312.23(a)(8).) If the results are promising and no disqualifying safety

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[4] FDA, *What We Do* <https://www.fda.gov/about-fda/what-we-do>.

[5] *See* PhRMA, *Biopharmaceutical Research & Development: The Process Behind New Medicines* (2015) p. 14 <http://phrma-docs.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf>.

[6] *See* FDA, *Development and Approval Process (Drugs)* <http://www.fda.gov/Drugs/DevelopmentApprovalProcess> (as of Oct. 24, 2024) (FDA's drug approval process "ensures that drugs, both brand-name and generic, work correctly and that their health benefits outweigh their known risks"); 21 U.S.C. § 355(d).

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issues are identified, the company – referred to as the "Sponsor" – submits an Investigational New Drug Application ("IND") to FDA, outlining the preclinical study results and offering a plan for clinical trials in humans. (21 U.S.C. § 355(i)(2); 21 C.F.R. § 312.20(a)–(b).)

FDA carefully reviews the contents of the IND, both analyzing the preclinical data generated by the Sponsor to date and evaluating the Sponsor's proposed plan of clinical study. These clinical studies proceed in "phases," each of which must be completed successfully before the potential new medicine may undergo FDA review and, ultimately, approval. (21 C.F.R. § 312.21.) On average, the clinical trial phase of a drug's development pathway takes six to seven years to complete.[7] If the drug satisfies the pre-determined goals of its clinical program as set forth in the IND, the Sponsor will package up all of the data, including compiling extensive statistical analyses and safety assessments, and submit a New Drug Application ("NDA") to FDA for consideration. (21 U.S.C. § 355(b).) If after reviewing this data FDA determines that the medicine's benefits outweigh its risks as administered under the conditions of the approved Prescribing Information, FDA will permit a manufacturer to market the medicine by approving the NDA.

These three phases of clinical testing vary greatly in scope and scale, and in the information that can be gleaned at each stage.[8] Phase I trials are generally conducted on a small number of healthy volunteers – not patients with the target disease – to allow the sponsor to help assess

[7] PhRMA, *Modernizing Drug Discovery, Development and Approval* (2016) p. 1 <http://phrma-docs.phrma.org/sites/default/files/pdf/proactive-policy-drug-discovery.pdf>.

[8] *See* PhRMA, *Biopharmaceutical Research & Development: The Process Behind New Medicines* (2015) p. 16, <https://www.phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/P-R/rd_brochure.pdf>.

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pharmacokinetics (how the drug is absorbed and metabolized), pharmacodynamics (the drug's impact on the body), and tolerability. Phase II studies usually begin to study the medicine in patients with the target disease, typically small in number, to begin to gather data on impact on the disease state and potential dosing, and to identify any potential unanticipated safety issues or "off-target" effects. Significant and unanticipated off-target effects – where the drug candidate unexpectedly impacts another part of the body aside from the targeted system – often will doom a medicine's development. If Phase I and Phase II studies do not yield positive results, the drug will not move forward to Phase III trials.

Crucially for the Court's evaluation of this case, early phase clinical trials typically are not intended or designed to provide definitive conclusions regarding efficacy and safety and could not be used to make any meaningful comparison to the safety and efficacy of an approved medicine.[9] At this early stage of development, companies do not "know" that a medicine is "safer" or "at least as equally effective" as some other approved medicine. Here, Gilead performed a single Phase I / Phase II combined clinical study of TAF that tested only 30 patients over the course

[9] In certain circumstances where there is an unmet medical need for patients suffering from serious conditions, FDA can approve a drug with "accelerated approval" based on trials that show the drug has an effect on "surrogate endpoints" which are thought to predict clinical benefits, but are not themselves a measure of clinical impact, or based on certain intermediate endpoints. (21 C.F.R. § 314.510.) To be clear, the 30-patient preliminary Phase I/II combined trial in this case was not part of any such approach. *See generally* FDA, *Accelerated Approval* (Feb. 24, 2023) <https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval>; Lowe, *Accelerated Approval: What is it Accomplishing?* Science (Oct. 17, 2024) <https://www.science.org/content/blog-post/accelerated-approval-what-it-accomplishing>.

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of a mere 14 days. (Petitioner's Opening Brief 14-15.)[10] In a trial of 30 participants, the resulting data would not have the power to discern true differences between the two treatment groups, nor would the patient population be anywhere near the number needed to detect any but the most common adverse reactions.

B. The Role of Phase III Clinical Trials in Establishing the Risk/Benefit Profile of a Medicine.

Unlike earlier phase studies, Phase III "pivotal" clinical trials are the traditional vehicle by which a Sponsor and the FDA can make a considered scientific determination as to the safety and efficacy – or risk/benefit profile – of a new medicine.[11] Phase III studies are randomized, controlled clinical trials that typically involve hundreds or thousands (and sometimes tens of thousands) of subjects and often run for months or years. They are designed to be appropriately powered to detect differences between the drug candidate and the comparator, whether it be a placebo or a different treatment. The large number of subjects also allows for the detection of rarer side effects that might not have been seen in earlier, smaller-scale human testing.

Phase III trials require the investment of substantial resources. Manufacturers sponsoring clinical trials work with healthcare providers, often at major research institutions, who serve as clinical investigators. They must also put procedures in place to coordinate with dozens and

[10] In certain therapeutic areas, including cancer and other serious conditions, a Sponsor can combine Phase I and Phase II objectives into a single trial. National Cancer Institute, *Phase I/II Clinical Trial*, <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/phase-i-ii-clinical-trial> ("Combining phases I and II may allow research questions to be answered more quickly or with fewer patients.").

[11] *See* FDA, *The Drug Development Process: Step 3: Clinical Research* <https://www.fda.gov/patients/drug-development-process/step-3-clinical-research>.

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sometimes hundreds of institutions to carefully monitor the participants and meticulously gather and document the necessary data.[12]

The data that comes out of Phase III trials allow a rigorous scientific assessment of the safety and efficacy of the drug candidate. In most situations, there is no juncture prior to the completion of large Phase III trials and FDA approval at which a biopharmaceutical company can be expected to reasonably "know" that a medicine is safe and effective. But more importantly for this case, even Phase III trials generally do not permit the kind of *comparative* assessment that the Court of Appeal said should be the foundation of tort liability. Most Phase III trials are placebo-controlled trials, meaning the treatment is being compared to a sugar pill or similar inactive administration. This data would not allow a company to make any comparative assessment against any other medicine, whether marketed or not. Indeed, the FDA has strict rules prohibiting these kinds of comparative assessments not supported by actual head-to-head trials comparing the two treatments. (21 C.F.R. § 202.1(e).)

In some cases, the new drug candidate is tested against an existing standard-of-care treatment, e.g., when medical ethics would not allow the subjects to forego an existing treatment. Under such circumstances, new medicines can be (and typically are) approved when they are demonstrated to be generally equivalent in efficacy, or in FDA terms, "non-inferior."[13]

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[12] *See* National Institutes of Health, *NIH Clinical Research Trials and You: The Basics* <https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics>.

[13] *See* FDA, *Non-Inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry* (Nov. 2016) <https://www.fda.gov/media/78504/download> ("The usual reason for using a [non-inferiority] active control study design instead of a superiority design is an ethical one. Specifically, this design is chosen when it would not be ethical to use a placebo, or a no-treatment control, or a very low dose of an active drug, because there is an effective treatment that provides an

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At some point in the lifecycle of a medicine, a company may be able to determine whether a medicine is equally effective and less risky *on a population basis* than an alternative, but it is rarely before a medicine is placed on the market and certainly not before head-to-head clinical trials are conducted.

And there's another problem. Even assuming a head-to-head trial that shows differences on a population level, it is impossible for biopharmaceutical companies to *ever* know whether a new medicine is safer and equally effective for any specific individual patient. Each potential patient has a different genetic makeup and a unique set of environmental exposures that may impact how a drug works for the patient. Separately, each potential patient may have a different conception about what "safer" means. Patients weigh the significance of different potential adverse effects in light of factors specific to their life and family circumstances and may therefore have differing tolerances for different kinds of risks. For instance, a patient on an anticoagulant (blood thinner) faces an increased risk of bleeding complications but will also have a reduced risk of suffering a stroke. How patients weigh these two safety risks will vary on their age and overall health profile.

The effectiveness of medicines will also vary greatly depending on the characteristics of individual patients. Even where two medicines are shown to have identical rates of efficacy on a population basis, that does not mean that they will be equally effective for every potential individual patient. Few medicines are effective for every patient who takes them, and one patient may succeed on one medicine but not another. There are numerous examples of this phenomenon among some of the most common

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important benefit (e.g., life-saving or preventing irreversible injury) available to patients for the condition to be studied in the trial.")

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medical problems patients face. Psychiatrists often have to go through a process of trial and error to find a specific antidepressant medicine that will work with a particular patient.[14] The same is true for Type 2 diabetes medicines, with doctors using trial-and-error among the commonly prescribed medicines to find one that works for the particular patient.[15] So too, for doctors trying to find an effective medicine to treat high blood pressure.[16] The reason prescription medicines are available by prescription only is that it takes the skill and individualized attention of a clinician to determine the risk/benefit balance for any given patient. (*See Brown v. Superior Court*, (1988) 44 Cal.3d 1049, 1061 ("A physician appreciates the fact that all prescription drugs involve inherent risks, known and unknown, and he does not expect that the drug is without such risks.").)

Thus, the central inquiry posed by the Court of Appeal – whether a company delayed development of an equally effective medicine with lower risks – is a concept both unknowable and fundamentally inconsistent with how drug development works. Here, even postulating that Gilead would

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[14] *See* Leuchter, et al., *A new paradigm for the prediction of antidepressant treatment response* (2009) 11 Dialogues Clin. Neuroscience 4 ("There are more than 20 treatments for [major depressive disorder] approved as effective by the Food and Drug Administration (FDA). The challenge is choosing the best treatment for each patient. . .. [I]t may take 1 to 2 years to identify the treatment that will get a patient well.").

[15] *See* Medical News Today, *Type 2 diabetes: Five genetic 'clusters' may explain evolution* (September 25, 2018) <https://www.medicalnewstoday.com/articles/323159> ("'When treating type 2 diabetes,' reports [Dr.] Jose Florez [of Harvard Medical School and Massachusetts General Hospital], 'we have a dozen or so medications we can use, but after you start someone on the standard algorithm, it's primarily trial and error.'").

[16] *See* Cleveland Clinic, *Resistant Hypertension* (Aug. 30, 2023) <https://my.clevelandclinic.org/health/diseases/15601-resistant-hypertension> ("Resistant hypertension is blood pressure that's higher than normal even though you're taking at least three different medicines for it at once. Most people with this condition can bring their blood pressure into a healthy range, but it may take some trial and error with medications.").

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have moved forward with further development and ultimately Phase III testing of TAF, the data derived for a placebo-controlled trial would not have allowed the kind of TDF/TAF safety-efficacy comparison envisioned by the Court of Appeal. And even if, in this hypothetical world, there would have been a head-to-head TDF/TAF trial, the overall population results would not have demonstrated for any specific patient a more effective or "safer" option. Thus, the fact that the Court of Appeal rested its duty on the results of a single early-phase, 30-person trial underscores how incongruous its analysis was.

II. The Court of Appeal Decision Does Not Consider the Realities of the Pharmaceutical Development Process.

There is no need for new legal duties and negligence theories where biopharma manufacturers are already strongly incentivized to bring innovative medicines to market in a safe and expedient manner. The problem is that at very nascent stages in the drug development process, it is impossible to tell which compounds will succeed and which will fail. The Court of Appeal constructs a false narrative in which companies have some sense of certainty after preliminary studies that a drug will be successful. They most certainly do not, but even if so, companies have every incentive to bring promising drugs forward quickly. There is a significant first-mover advantage and sitting on a safe and effective medicine is a nonsensical economic decision by a biopharmaceutical company.

Instead, scrutinizing and second-guessing decisions made in the early stages of clinical testing will lead to a dramatic chilling effect on the creation of new and innovative medicines. Under the regime endorsed by the Court of Appeal, companies could choose to wait until all potential alternatives fail before seeking FDA approval for a medicine, for fear that they bet on the wrong candidate, or they could choose to cease working on next-generation improvements once the initial drug gets approved, for fear

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a subsequent candidate might turn out to perform better on some metric and open up the company to lawsuits like this one. Both alternatives are bad, and stifling development of related compounds especially will do a great disservice to patients given the long history of groundbreaking next-generation pharmaceutical innovations.

It is also not foreseeable under *Rowland* that a drug would be "harming" patients based on the initial results from a preliminary Phase I/II trial. The Court of Appeal mistakenly assumed in its *Rowland* inquiry that FDA approval can be confidently predicted at this early stage despite the reality that drugs frequently fail to gain approval even after Phase III trials. Of the drugs that make it through Phase I and Phase II, FDA estimates that only 25-30% will successfully make it past Phase III.[17] Promising early results on a small sample size of subjects hardly makes it foreseeable that a drug will be approved for use, much less that such a drug will outperform another in terms of both safety and efficacy.

A. Existing Dynamics Incentivize Companies to Bring Promising Compounds to Market Promptly.

Given the dynamic market competition in the pharmaceutical industry, and the steady pace of scientific advances, companies are already discouraged from delaying the development of potentially beneficial medications. Drug manufacturers have a financial incentive to deliver innovative, safe, and effective treatments to patients as expeditiously as possible. The drug development industry is extremely competitive, where the first company to bring a new innovative treatment to patients can make significant inroads in a given therapeutic area. The pace of innovation is

[17] FDA, *The Drug Development Process: Step 3: Clinical Research* <https://www.fda.gov/patients/drug-development-process/step-3-clinical-research> (noting that 70% of drugs that enter Phase I move forward, 33% for Phase II, 25-30% for Phase III).

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also constant and complex, requiring companies to constantly focus on research and development. Companies have every incentive to develop and deliver safe new medicines as quickly as possible because of the "first mover" dynamics in the pharmaceutical industry.[18]

The decision of the Court of Appeal creates a new duty and corresponding negligence liability to fix a problem that does not exist, and completely ignores the existing market forces which already drive rapid, safe innovation. The benefit that patients and a company gain from FDA approval of advances in treatments far outweighs any speculative advantage a company might receive from delaying development to benefit its existing products on the market. Any supposedly nefarious decision not to move forward with development of a promising drug risks the strong possibility that a rival will introduce a further advance that would eliminate any purported advantage from such a delay strategy.

The case of TAF itself illustrates the example. If it was indeed established that TAF was safer or more effective than TDF in 2004, Gilead would have had every reason to pursue development as quickly as possible and reap the significant market benefit of delivering such a medical advance. This immediate benefit would dramatically outweigh any marginal and speculative benefit that could be obtained by delaying FDA approval of TAF. (Petitioner's Opening Brief 18-19; Petitioner's Reply Brief 13-14).

B. The Lack of Foreseeability That Exists at Early Development Stages Precludes Liability.

Foreseeability is critical to the Court of Appeal's decision to reject an exception to duty under *Rowland*, but the Court of Appeal made several

[18] Erin Medlyn, *Why Launching a New Drug First is Key* (Sept. 15, 2015) <https://www.weforum.org/agenda/2015/09/why-launching-a-new-drug-first-is-key/>.

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unsupported inferential leaps to reach this conclusion. The Court of Appeal emphasized that "foreseeability of injury" is the most critical *Rowland* factor, yet rested that foreseeability assessment on the manufacturer's knowledge that the new medicine would be safer and equally effective than the existing drug. (Op. 41-42.) The Court of Appeal bootstrapped this presumed knowledge to reject the notion that FDA approval is highly uncertain at early stages of drug development. (Op. 42-43.) Respectfully, such a dramatic expansion of liability should not rest on so circular and tenuous an assumption.

In reality, the paramount characteristic of the drug development process is the exact opposite of foreseeability: uncertainty. Just one out of every 5,000 or 10,000 compounds under development, and less than one out of every eight medicines entering clinical trials, ultimately obtains FDA approval.[19] For example, between 1998 and 2019, three new brain cancer treatments achieved FDA approval, with 122 unsuccessful attempts.[20] Similarly, out of 268 attempts to develop lung cancer treatments over the same period, the FDA ultimately approved 32 medicines.[21]

Indeed, more than half of the medicines that show promise in early clinical trials will fail in Phase III trials.[22] Many more do not make it to

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[19] PhRMA, *Clinical Trials—So Necessary but More Complex than Ever* (Mar. 3, 2011) <https://catalyst.phrma.org/clinical-trials-so-necessary-but-more-complex-than-ever>.

[20] *Biopharmaceuticals in Perspective*, *supra* note 4, at p. 40.

[21] *Ibid.*

[22] *See* Hwang, et al., *Failure of Investigational Drugs in Late-Stage Clinical Development and Publication of Trial Results*, 176 JAMA Internal Med. 1826 (2016) ("Roughly half of investigational drugs entering late-stage clinical development fail during or after pivotal clinical trials, primarily because of concerns about safety, efficacy, or both."); *see also* FDA, *Step 3: Clinical Research* <https://www.fda.gov/patients/drug-development-process/step-3-clinical-research#Clinical_Research_Phase_Studies>.

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Phase III at all because of underwhelming results in Phase I and Phase II testing. Even Phase III trials that are considered "confirmatory" of promising Phase I and Phase II trials fail at a rate of 50%, indicating that early-stage trials of the sort implicated here generally cannot provide the type of definitive information regarding overall safety and efficacy that the Court of Appeal conjectured.[23]

The heartbreaking setbacks encountered over the last two decades in researching and developing treatments for Alzheimer's disease perhaps present the most striking illustration of how early promise does not guarantee Phase III success.[24] For example, an early study of nilvadipine, traditionally used to treat hypertension, showed improvements in cognitive tasks and executive function in an 85-patient study. However, the drug failed to demonstrate efficacy in a 1.5-year, 500-person Phase III trial.[25] In addition, pioglitazone, a diabetes medicine, showed cognitive and functional improvements in two trials of Alzheimer's patients totaling 74 subjects. However, Phase II testing was less promising, and the drug failed outright in a large, 3,500-patient Phase III study.[26] By contrast, sometimes medicines exceed expectations when the Phase III results come in. The revolutionary results of novel oral anticoagulants turned out to provide

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[23] Pretorius, et al., *Phase III Trial Failures: Costly, But Preventable, Applied Clinical Trials* (Aug. 1, 2016) <https://www.appliedclinicaltrialsonline.com/view/phase-iii-trial-failures-costly-preventable> ("What is unexpected, however, is the percentage of "confirmatory" Phase III trials that fail-about 50%. Theoretically, if early-phase trials provide the necessary criteria for moving a drug program to Phase III testing, relatively few Phase III trials should fail; but that is not the case.").

[24] *See* Kim, et al., *Alzheimer's Disease: Key Insights from Two Decades of Clinical Trial Failures*, J. Alzheimer's Dis. 87 (2022) (since 2003, 98 unique Phase II and Phase III compounds failed, compared with just two reported Phase III successes).

[25] *Ibid*.

[26] *Ibid*.

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remarkable (and unexpected) improvements over warfarin, which had been the standard of care for 50 years.[27]

As FDA recognizes, "it is not known whether [a] potential medical treatment offers benefit to patients until clinical research on that treatment is complete."[28] Recent history is full of examples of high-profile Phase III failures when earlier-phase studies showed promising results. To name only a few:

- Mirati Therapeutics' Phase III SAPPHIRE trial failed to improve the overall survival rate in a study of patients with non-small cell lung cancer, causing the company to discontinue development.[29]
- Bayer halted the Phase III trial of its factor XI inhibitor asundexian early after it showed a lack of superior efficacy compared to another medicine for the prevention of stroke and systemic embolism in patients with atrial fibrillation.[30]
- Merck KGaA's experimental multiple sclerosis compound known as evobrutinib failed to meet its primary goals in two

[27] *See* Biswas, et al., *Present Knowledge on Direct Oral Anticoagulant and Novel Oral Anti Coagulants and Their Specific Antidotes: A Comprehensive Review Article*, 48 Current Problems in Cardiology 2 (2023) ("The development of these new agents represents a landmark and revolutionary development in the therapy for [venous thromboembolisms].").

[28] FDA, *Conducting Clinical Trials* <https://www.fda.gov/drugs/development-approval-process-drugs/conducting-clinical-trials>

[29] Manalac, *Mirati's Sitravatinib Fails in Phase III Lung Cancer Trial, Nixes Development*, Biospace (May 25, 2023) <https://www.biospace.com/mirati-s-sitravatinib-fails-in-phase-iii-lung-cancer-trial-nixes-development>.

[30] Hughes, *Asundexian Phase 3 Study Halted for Lack of Efficacy*, Medscape (Nov. 20, 2023) <https://www.medscape.com/viewarticle/998665?form=fpf>.

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highly anticipated Phase III trials, showing no improvement over the control medicine.[31]

- Janssen Pharmaceuticals discontinued its Phase III Mosaico HIV vaccine clinical trial due to a lack of efficacy in a 3,900-person study.[32]

It is thus facially wrong to presume, as the Court of Appeal did, that the FDA will approve a drug that makes it into Phase III clinical testing. (Op. 56.) Positive early phase results are more accurately viewed as the ticket to entry into full Phase III testing, not the marker of ultimate success. After all, no company would ever invest in resource-intensive Phase III studies in the absence of such promising data, but the extremely high rate of Phase III failures directly rebuts the Court of Appeal's speculation that success in Phase III can be presumed when positive early-stage data exists. Indeed, even where a company "reasonably believes" that the data from its Phase III trials support approval, FDA in its scientific judgment frequently will disagree, declining approval and requiring the company to conduct further studies.[33] The notion that one can foreseeably predict success in

[31] Burger, *Merck KGaA suffers major blow as MS drug fails in late-stage trials*, Reuters (Dec. 6, 2024) <https://www.reuters.com/business/healthcare-pharmaceuticals/merck-kgaa-says-ms-drug-fails-late-stage-trials-2023-12-05/>.

[32] Johnson & Johnson, *Janssen and Global Partners to Discontinue Phase 3 Mosaico HIV Vaccine Clinical Trial*, (Jan. 18, 2023) <https://www.jnj.com/media-center/press-releases/janssen-and-global-partners-to-discontinue-phase-3-mosaico-hiv-vaccine-clinical-trial>.

[33] *See, e.g.*, Sacks, et al., *Scientific and Regulatory Reasons for Delay and Denial of FDA Approval of Initial Applications for New Drugs, 2000-2012* (January 22/29, 2014) 311 JAMA 4 <https://jamanetwork.com/journals/jama/fullarticle/1817795> (out of 302 drug applications submitted to the FDA between 2000 and 2012, 80 (26.5%) were never approved, with an additional 71 (23.5%) requiring one or more re-submissions, resulting in a median delay of approval of 435 days).

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pivotal trials just because there is promising Phase I/II data finds no support in the real world.

But the Court of Appeal's logical leaps went even further. As noted above, medicines are not typically tested against each other even in Phase III trials to establish comparative safety or efficacy under FDA's rigorous standards for comparative claims. FDA approval requires that the medicine be shown safe and effective on its own terms, not that its benefits or risks compare favorably to those of some other real or hypothetical product. (21 U.S.C. § 355(c).) It is thus even less foreseeable that a second compound will turn out not only to obtain regulatory approval, but then to be proven "better" than an existing approved medicine. Yet that is the supposedly "foreseeable" outcome upon which the Court of Appeal's decision rests.

C. The Liability Created by the Court of Appeal Will Stifle Innovation.

The danger of the Court of Appeal's decision is not just that it ignores the existing realities and incentives in the pharmaceutical market, but also that the decision would skew the incentives in the opposite direction and actually deter biopharma investment and innovative research. Penalizing companies for not bringing forward every compound – essentially for guessing wrong in their development resource allocation decisions – creates perverse incentives that would inhibit the best new medicines from coming to market.

Biopharmaceutical companies constantly face the reality that promising prospective drugs may fail, requiring a robust pipeline of alternative and backup candidates to hedge against. Given the risk of failure inherent in the development of new medicines, life sciences companies often develop multiple medicines in parallel. Companies must make complicated strategic decisions about where to devote resources based on limited information about which medicines have the most

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promise. Over 8,000 potential new medicines are under study today, with PhRMA's, BIO's, and CLS's members making extraordinary investments in research and development.[34] Phase III testing in particular is remarkably expensive and accounts for the highest category of research and development expenditure for PhRMA members.[35] In mapping out their research and development plans in such an uncertain and fraught environment, biopharmaceutical companies must allocate resources based on imperfect information, and given the uncertainty often by necessity have to make educated guesses as to where best to devote resources across the range of compounds being developed in parallel. Imposing a negligence liability regime for guessing wrong, or punishing companies for not bringing forward every compound that shows mild early promise through Phase III, will actually discourage the identification and exploration of such backup compounds.

For example, consider the biopharmaceutical company deciding whether to invest resources into researching different compounds for treating a particular disease. While it might make scientific and practical sense to focus on one of those compounds as the best candidate to deliver an effective treatment in the shortest amount of time, the company might have second thoughts about such a singular focus if it knows it could face

[34] *Biopharmaceuticals in Perspective*, *supra* note 4, at p. 20 (noting that PhRMA members invest nearly one-quarter of their total annual domestic sales revenue in R&D).

[35] *See* Sertkaya, et al., *Key cost drivers of pharmaceutical clinical trials in the United States*, 13 Clin. Trials 2 (2016) (noting that average Phase III study cost between $11.5 million for dermatology to $52.9 million for anesthesia and describing the clinical and administrative costs of such studies); *2024 PhRMA Annual Membership Survey* (2024) p. 4 tbl. 3 <https://phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Refresh/Report-PDFs/PhRMA_2024-Annual-Membership-Survey.pdf>.

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liability if it makes the wrong choice and another of the candidates turns out later to be a "better" option.

Consider alternatively the biopharmaceutical company that has already developed a safe and effective medicine whose benefits outweigh its risks. The medicine has proven itself in clinical trials, and secured FDA approval. But the company knows that the medicine, like all medicines, carries risks. The company could continue research efforts to develop alternative treatments with apparently comparable benefits but perhaps fewer risks. However, under the Court of Appeal's decision, every patient who took the original medicine is potentially a plaintiff if the company succeeds in making a further medical advance, as the company could be accused of not commercializing the alternative quickly enough.

Against that backdrop, a company might be incentivized to wait to bring the original, first medicine to market until research into all possible compounds under investigation for a particular treatment has been exhausted, even if that delay lasts years or decades. (*Brown*, *supra* 44 Cal.3d at 1063.) Alternatively, the company might decide to halt research into potentially "better" therapies once the first medicine is approved for fear that it succeeds and becomes liable to every patient who benefitted from the original medicine. Both outcomes would be detrimental to public health. If the innovator elects the former strategy – wait to seek approval until all alternatives for a better candidate are exhausted – and research into other compounds does not pan out, nothing will stop creative plaintiffs using the rationale of the Court of Appeal from accusing the company of negligence for delaying the delivery of a beneficial treatment in the interim.

Patient welfare would suffer dramatically from those misaligned incentives. History is replete with examples of incremental reformulations of FDA-approved medicines that dramatically improved public health. On average each year, approximately two-thirds of global launches of new

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molecular entities involve improvements to existing molecules.[36] Further, 63 percent of medicines on the World Health Organization's Essential Drug Lists are follow-on innovations.[37]

Recent history demonstrates that innovations involving previously FDA-approved medicines dramatically improve public health. New formulations for malaria medicine have decreased dosing from eight daily tablets to two; the combination of two medicines into a single dosage form has eased the strict treatment regimen for Type 2 diabetes; and research into oral contraceptives has resulted in lower-estrogen formulations with dramatically reduced side effects.[38] Another example is treatment for hepatitis C, a chronic viral infection affecting up to 170 million people worldwide that can result in liver failure, liver cancer, and even death. In the 1990s, treatment for hepatitis C often involved conventional interferon alfa, a regimen that required between three and seven weekly injections to achieve cure rates of 38 to 43 percent.[39] By 2001, scientific discoveries led one manufacturer to modify the conventional interferon alfa molecule to

[36] Int'l Fed. of Pharm. Mfrs. & Ass'ns, *Incremental Innovation: Adapting to Patient Needs* (2016) p. 11 fig.3 < https://www.ifpma.org/wp-content/uploads/2023/01/i2023_IFPMA_Incremental_Innovation_Feb_2013_Low-Res.pdf>.

[37] Cohen & Kaitin, *Follow-On Drugs and Indications: The Importance of Incremental Innovation to Medical Practice*, 15 Am. J. Therapeutics 89, 90 (2008).

[38] Globerman & Lybecher, *The Benefits of Incremental Innovation: Focus on the Pharmaceutical Industry* (2014) pp. 46–48 <https://www.fraserinstitute.org/sites/default/ files/benefits-of-incremental-innovation.pdf>.

[39] Int'l Fed. of Pharm. Mfrs. & Ass'ns, *Incremental Innovation: Adapting to Patient Needs* (2016) p. 19 < https://www.ifpma.org/wp-content/uploads/2023/01/i2023_IFPMA_Incremental_Innovation_Feb_2013_Low-Res.pdf>.

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slow down its absorption rate, resulting in once-weekly dosing with a substantially higher efficacy rate (56 percent).[40]

These later scientific breakthroughs do not discredit earlier scientific discoveries. Scientific knowledge is ever evolving, and later scientific discoveries often build on prior advances. California's liability regime should encourage these discoveries, not penalize researchers for continuing to improve on existing treatments. Imposing liability for scientific and business judgment calls on resource allocation would have a dangerous chilling effect on the biomedical research conducted by amici's members. Doing so would impede needed treatments from reaching patients and impact a significant California industry.

Nor is the liability framework embraced by the Court of Appeal necessary to protect patients. FDA has extraordinary oversight and authority over the actions of biopharmaceutical companies, and this extensive existing regulatory regime protects the interests of patients to help ensure the quickest access to the advanced treatments demonstrated to be safe and effective. In the case at hand, TDF remains approved by FDA as a safe and effective treatment, and the Plaintiffs have agreed that TDF is not in any way defective. By endorsing Plaintiffs' theory and allowing patients who have taken TDF – a fully-approved, non-defective medicine – to pursue a lawsuit for not having earlier access to TAF, the Court of Appeal's decision fundamentally undermines the federal regulatory agency statutorily entrusted to make this fundamental risk-benefit determination. Respectfully, this Court should have grave doubts about authorizing such a pathway for liability.

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[40] *Id.* at 21; *see also* Lietzan, *Paper Promises for Drug Innovation* (2018) 26 Geo. Mason L. Rev. 168, 175–76.

CONCLUSION

Given the goals and limitations of the early-stage FDA clinical trials at issue here, it was not feasible for Gilead to "know" at that point whether TAF would turn out to be sufficiently safe and effective to warrant regulatory approval. Even with Phase III testing, the comparative benefit of one medicine over another can only be established by head-to-head tests that are not required for FDA approval, making any foreseeability analysis inherently speculative. Ultimately, expanding liability in the manner Plaintiffs request will disincentivize the development of innovations in medicine and harm public health.

Respectfully submitted,

/s/ Ashley M. Simonsen

Ashley M. Simonsen
Alice L. Phillips
COVINGTON & BURLING LLP
1999 Avenue of the Stars
Los Angeles, CA 90067
Telephone: (424) 332-4782
Facsimile: (424) 332-4749
asimonsen@cov.com
aphillips@cov.com

Michael X. Imbroscio
COVINGTON & BURLING LLP
850 Tenth Street NW
Washington, DC 20001
Telephone: (202) 662-5694
Facsimile: (202) 778-5694
mimbroscio@cov.com

Gregory L. Halperin
COVINGTON & BURLING LLP
620 Eighth Avenue
New York, NY 10018
Telephone: (212) 841-1166

Document received by the CA Supreme Court.

Facsimile: (646) 441-9166
ghalperin@cov.com

Counsel for Amici Curiae Pharmaceutical Research and Manufacturers of America, Biotechnology Innovation Organization, and California Life Sciences

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This brief complies with the type-volume limitations of Appellate Rules 8.520(c)(1) because it contains 7,289 words, as counted by the Microsoft word-processing program used to prepare the brief, excluding the parts of the brief exempted by Appellate Rule 8.520(c)(3).

/s/ Ashley M. Simonsen
Ashley M. Simonsen
Counsel for Amici Curiae Pharmaceutical Research and Manufacturers of America, Biotechnology Innovation Organization, and California Life Sciences

Dated: November 4, 2024

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PROOF OF SERVICE

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BRIEF OF THE PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA, BIOTECHNOLOGY INNOVATION ORGANIZATION, AND CALIFORNIA LIFE SCIENCES IN SUPPORT OF PETITIONER

on the interested parties in this action as follows:

GRANT & EISENHOFFER P.A.
M. Elizabeth Graham
2325 Third Street, Suite 329
San Francisco, California 94107
Telephone: (415) 229-9720
Email: egraham@gelaw.com

JENNER LAW, P.C.
Robert K. Jenner
3600 Clipper Mill Road, Suite 240
Baltimore, Maryland 21211
Telephone: (410) 413-2155
Email: rjenner@jennerlawfirm.com

MOSKOVITZ APPELLATE TEAM
Myron Moskovitz
90 Crocker Avenue
Oakland, California 94611
Telephone: (510) 384-0354
Email: myronmoskovitz@gmail.com

KERSHAW, COOK & TALLEY, P.C.
William A. Kershaw
401 Watt Avenue, Suite 1
Sacramento, California 95864
Telephone: (916) 779-7000
Email: bill@kctlegal.com

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SCHNEIDER WALLACE COTTRELL
KONECKY LLP
Amy Eskin
2000 Powell Street, Suite 1400
Emeryville, California 94608
Telephone: (510) 740-2936
Email: aeskin@schneiderwallace.com

ESNER, CHANG & BOYER
Andrew N. Chang, SBN 84544
Holly N. Boyer, SBN 221788
234 East Colorado Boulevard, Suite 975
Pasadena, California 91101
Telephone: (626) 535-9860
Email: achang@ecbappeal.com
hboyer@ecbappeal.com

THE LAWRENCE LAW FIRM
Jeffrey Lawrence
Levi's Plaza
1160 Battery Street East, Suite 100
San Francisco, CA 94111
(415) 685-5030
jeffreyl@jlawrencelaw.com

BURG SIMPSON ELDREDGE HERSH
& JARDINE, P.C.
Seth A. Katz
40 Inverness Drive East
Englewood, CO 80112
(303) 792-5595
skatz@burgsimpson.com

WASHINGTON LEGAL FOUNDATION
2009 Massachusetts Avenue,
NW Washington, DC 20036
Cory L. Andrew
John M. Masslon II
(202) 588-0302
candrews@wlf.org

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INTERNATIONAL CENTER FOR LAW
& ECONOMICS
Geoffrey A. Manne
Kristen Stout
Jeremy Kidd
1104 NW 15th Avenue, Suite 300
Portland, OR 97209
(503) 770-0076
kstout@laweconcenter.org

QUINN EMANUEL URQUHART
& SULLIVAN, LLP
John M. Potter, Esq.
50 California Street, 22nd Floor
San Francisco, CA 94111
(415) 875-6600 johnpotter@quinnemanuel.com

WILMER CUTLER PICKERING
HALE AND DORR LLP
Joseph Meyer
Thomas G. Saunders
Gary M. Fox
2100 Pennsylvania Ave.,
NW Washington, DC 20037
(202) 663-6000
joseph.meyer@wilmerhale.com
thomas.saunders@wilmerhale.com
gary.fox@wilmerhale.com

BOWMAN AND BROOKE LLP
Paul A. Alarcon, Esq.
600 Anton Boulevard, Suite 650
Costa Mesa, CA 92626
Telephone: (310) 380-6500
paul.alarcon@bowmanandbrooke.com

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O'MELVENY & MYERS LLP
Charles C. Lifland, Esq.
Sabrina H. Strong, Esq.
Jeffrey L. Fisher, Esq.
Jason Zarrow, Esq.
400 South Hope Street
18th Floor
Los Angeles, CA 90071
(213) 430-6000
clifland@omm.com

GUTIERREZ PRECIADO HOUSE
Calvin R. House, Esq.
3020 East Colorado Boulevard
Pasadena, CA 91107
(626) 449-2300
calvin.house@gphlawyers.com

GIBSON, DUNN & CRUTCHER LLP
Theane Evangelis, Esq.
Daniel Adler, Esq.
333 South Grand Avenue
Los Angeles, CA 90071
(213) 229-7000
dadler@gibsondunn.com

GHOST AUTONOMY INC.
Seth Travis
900 Villa Street
Mountain View, CA 94041
sethatravis@gmail.com

ATLANTIC LEGAL FOUNDATION
Lawrence S. Ebner
1701 Pennsylvania Ave.
Suite 200
Washington, D.C. 20006
(202) 349-1421
Lawrence.ebner@atlanticlegal.org

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PAUL, WEISS, RIFKIND, WHARTON &
GARRISON LLP
Randy Luskey
Kannon K. Shanmugam
535 Mission Street, 24th floor
San Francisco, CA 94105
(628) 432-5112
rluskey@paulweiss.com

ORRICK, HERRINGTON & SUTCLIFFE LLP
E. Joshua Rosenkranz
Andrew Silverman
Elizabeth Bixby
51 West 52nd Street
New York, NY 10015
Telephone: (212) 506-5000
Facsimile: (212) 506-5151
jrosenkranz@orrick.com
asilverman@orrick.com
ebixby@orrick.com

[x] (BY TRUEFILING) By filing and serving the foregoing through Truefiling such that the document will be sent electronically to the eservice list on November 4, 2024;

I declare under penalty of perjury under the laws of the State of California that the foregoing is true and correct and that this proof of service is executed at Washington, D.C. on November 4, 2024.

/s/ Anand Balaji
Anand Balaji

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