No. 18-97

IN THE

Supreme Court of the United States

MARION LIU,

Petitioner,

v.

JANSSEN RESEARCH & DEVELOPMENT, LLC,

Respondent.

ON PETITION FOR A WRIT OF CERTIORARI TO THE CALIFORNIA COURT OF APPEAL, SECOND APPELLATE DISTRICT, DIVISION FIVE

REPLY BRIEF

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THIS COURT PROPERLY HAS JURISDICTION OF THE ISSUE PRESENTED

The primary – indeed the only – argument presented by Respondent Janssen Research and Development, LLC ("Janssen") for denying certiorari is its assertion that this Court has no jurisdiction because no federal issue was raised by Petitioner Marion Liu ("Liu") in the trial court, the California Court of Appeal or the California Supreme Court.

That assertion, however, is undermined by Janssen's own Appendix submitted in support of its Opposition. At page App. 24 of its Appendix, Janssen provides the "Issues" presented by Liu to the California Supreme Court. The very first sentence of the very first issue states: "The Court of Appeal recognized in this case that '*FDA regulations* impose a duty on a drug company testing its drugs on humans to 'monitor the progress of [its] studies to ensure compliance with study protocols and the health and safety of participants.' (Opinion, p. 17.)" But, the issue presented goes on to explain that, despite those FDA regulations, the appellate court failed to honor the mandates of the FDA regulations, concluding that despite them, drug companies are not required to intervene in ongoing malpractice committed by the drug company's own principal investigator. (Respondent's Appendix, p. App. 24.) The stated issue presented to the California Supreme Court then says: "Does a drug company have a duty to medically monitor the participants of its drug study, and can it thus be liable for its failure to exercise its independent power to stop a clinical study and refer a participant to medical care when it is aware that the participant is suffering from a life-threatening medical

condition making him unsuitable to participate in the study?" (*Ibid.*)

Furthermore, in a portion of the Petition for Review to the California Supreme Court not provided in Janssen's appendix, the Petition itself argued that the appellate court went astray when it chose to ignore the relevant federal regulations and to focus instead on the principal investigator's malpractice:

> *Janssen's misconduct is precisely the kind of misconduct specifically contemplated by the FDA regulations imposing a duty on drug companies to actively monitor every stage of their studies and which explicitly vests in the drug company the power to intervene in those studies to require the clinical investigator to comply with the study's mandates for safety.* [3RT571:14-578:9; 653:6-656:8; 4RT794:19-796:22; 798:3-11; 8RT1756:22-1759:2; 1756:22-1759:2; 1790:3-1798:4.] That standard was even confirmed by two of Janssen's own experts. [4RT898:26-899:7, 900:17-903:10; 10RT2156:20-2157:25; 2159:21-2161:10.] And that power, was expressly acknowledged by Janssen's own director of Global Clinical Trials after Leo's death: "Why [was] the patient . . . dosed despite the abnormal ECG screening? . . . Why was the project physician not contacted for discussion of the patient's eligibility prior to dosing since abnormal ECG?" [3RT660:8-661:15; 4RT906:6-13; 7RT1488:16-1489:8.]

> Rather than acknowledge this duty, the appellate court appears to have folded Janssen's clear misconduct into an inappropriate malpractice analysis, concluding that "JRD's undertaking as the drug study sponsor cannot reasonably be construed to include a 'guarantee of safety' from any and all acts of medical malpractice by physicians who bear the primary responsibility for safe-guarding the health of study participants." (Id., at 19.) Thus, *in contravention to federal law and clinical practice guidelines which require drug companies to independently monitor and protect the safety of study subjects, the appellate court concluded that drug companies are held entirely harmless from injury caused during drug trials, including affirmative acts of malfeasance.*

(Reply Appendix, pp. 3a-3b, emphasis added.)

Thus, the meaning and effect of federal regulations on human experimentation was squarely presented to the California Supreme Court.

Similarly, Liu argued extensively in her briefing to the Court of Appeal that FDA regulations imposed an independent duty on Janssen to continuously monitor the health and safety of the study subjects and to *intervene* when problems arose. (Reply Appendix, pp. 7a-12a.)[1]

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1. Janssen's assertion that this Court has no jurisdiction because Liu did not raise the FDA issues in her Petition for Rehearing to the Court of Appeal is a red herring. California appellate rules provide

And, as demonstrated in Petitioner's Appendix in support of her Petition for Writ of Certiorari, the parties extensively argued the meaning and effect of the FDA regulations to the trial court. (Petitioner's Appendix, pp. 35a-58a.)

Accordingly, Janssen's assertion that the issue was not sufficiently raised below is without merit.

Furthermore, as part of its jurisdictional argument, Janssen also contends that the Court of Appeal's opinion is based solely on an issue of state law and, as such, this Court does not have jurisdiction of the issue raised. (Respondent's Opposition, pp. 7-8.) In making that argument, however, Janssen creates an untenable "Catch 22" for litigants. Essentially, Janssen is arguing that even if a party asserts federal law as a basis for imposition of a duty of care, so long as a lower court rejects that analysis of federal law, the proponent of it has no basis for seeking relief from this Court. But a lower court's refusal to apply federal law should not abrogate this Court's power to interpret and construe the meaning and effect of that law. To do otherwise would mean that only the "winner" in the lower court, i.e., the party who successfully argued for application of the federal law, would have the power to obtain review of the issue by this Court – but, having

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that a Petition for Rehearing is optional, unless the appellate court's factual statements in its opinion are incomplete or misrepresentative, in which case a Petition for Rehearing is required in order to preserve factual arguments for Supreme Court review. California Rules of Court, Rule 8.500(c)(2); *Marriage of Goddard*, 33 Cal.4th 49, 53, n. 2 (2004); *Torres v. Parkhouse Tire Service*, 26 Cal.4th 995, 1000, n. 2 (2001). As such, Liu had no obligation to make any further *legal* argument regarding FDA regulations in the Petition for Rehearing.

won, why would they? Janssen's approach unreasonably limits a party's ability to obtain redress when a federal law is not properly considered or applied by a lower court.

And, in fact, Janssen's analysis is directly contradicted by the very authority it cites, *Illinois v. Gates*, 462 U.S.A 213, 218 n. 1(1983). As this Court stated in that footnote, this Court "developed the rule that a claim would not be considered here unless it had been *either* raised or squarely considered and resolved in state court." *Ibid.*, emphasis in original. Since the meaning and effect of the FDA's regulations regarding the duties of a drug study sponsor were, in fact, raised at every stage of the underlying litigation, this Court has jurisdiction to consider the issue.

Since Janssen's jurisdictional arguments are without merit, so is its request for sanctions. More importantly, having failed on its jurisdictional argument, and having ignored any other basis for denying certiorari, Janssen has necessarily conceded the importance of the issue presented.

Because Janssen's jurisdictional arguments are both substantively and procedurally without merit, they should be rejected and the requested relief should be granted.

CONCLUSION

For all the reasons stated, it is respectfully requested that Janssen's request for sanctions be rejected and that Liu's Petition for Writ of Certiorari be granted.

Respectfully submitted,

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September 2018

APPENDIX

APPENDIX A — EXCERPTS OF PETITION FOR REVIEW IN THE SUPREME COURT OF CALIFORNIA, DATED FEBRUARY 13, 2018

SUPREME COURT OF CALIFORNIA

MARION LIU, INDIVIDUALLY AND AS THE SUCCESSOR IN INTEREST TO AUGUSTINE LIU, SR

Plaintiff, Cross-Respondent and Petitioner,

vs.

JANSSEN RESEARCH & DEVELOPMENT, LLC,

Defendant and Cross-Appellant.

JUDGMENT OF THE SECOND DISTRICT COURT OF APPEAL, DIVISION 5 CASE NOS. B269318 / B270332 LOS ANGELES SUPERIOR COURT, CASE NO. BC432254

PETITION FOR REVIEW

[TABLES INTENTIONALLY OMITTED]

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ISSUES

ISSUE NO. 1: The Court of Appeal recognized in this case that "FDA regulations" impose a duty on a

drug company testing its drugs on humans to "monitor the progress of [its] studies to ensure compliance with study protocols and the health and safety of participants." (Opinion, p.17.) Nevertheless, the Court of Appeal held that drug companies do not owe a duty to the participants of the drug studies they design, create safety protocals for, and staff, for the participants' medical monitoring during the study because, the appellate court concluded, it is *unforeseeable* that the physicians retained by the drug company to conduct the study would act negligently. As such, the Court of Appeal relieved defendant Janssen Research & Development, LLC ("Janssen") of all liability for the harm it caused despite the jury's finding it had been negligent. The issue for this Court is therefore: Does a drug company have a duty to medically monitor the participants of its drug study, and can it thus be liable for its failure to exercise its independent power to stop a clinical study and refer a participant to medical care when it is aware that the participant is suffering from a life-threatening medical condition making him unsuitable to participate in the study?

ISSUE NO. 2: Is it for the jury, as a matter of fact, or for a court, as a matter of law, to decide whether the opinion of a qualified medical expert that, to a reasonable medical probability, a drug was a substantial factor in contributing to a plaintiff's injury or death is sufficient to establish causation?

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440, 449; s*ee Miles Labs., Inc. v. Superior Court* (1982) 133 Cal.App.3d 587, 595-596 [manufacturer liable for failure to warn of risks of off-label uses]. *Bunch v. Hoffinger Industries, Inc.* (2004) 123 Cal.App.4th 1278, 1302-1303; *Huynh v. Ingersoll-Rand* (1993) 16 Cal.App.4th 825, 833; *Wright v. Stang Mfg. Co.* (1997) 54 Cal.App.4th 1218, 1235.)

Curiously, despite reaching this holding of no duty, the Court of Appeal acknowledged that "FDA regulations impose on study sponsors a *general* duty to monitor the progress of their studies to ensure compliance with study protocols and the health and safety of participants…." (*Id.*, at 17.) Indeed, Janssen's misconduct is precisely the kind of misconduct specifically contemplated by the FDA regulations imposing a duty on drug companies to actively monitor every stage of their studies and which explicitly vests in the drug company the power to *intervene* in those studies to require the clinical investigator to comply with the study's mandates for safety. [3RT571:14-578:9; 653:6-656:8; 4RT794:19-796:22; 798:3-11; 8RT1756:22-1759:2; 1756:22-1759:2; 1790:3-1798:4.] That standard was even confirmed by *two of Janssen's own experts.* [4RT898:26-899:7, 900:17-903:10; 10RT2156:20-2157:25; 2159:21-2161:10.] And that power, was expressly acknowledged by Janssen's own director of Global Clinical Trials after Leo's death: "Why [was] the patient . . . dosed despite the abnormal ECG screening? . . . *Why was the project physician not contacted for discussion of the patient's eligibility prior to dosing since abnormal ECG*?" [3RT660:8-661:15; 4RT906:6-13; 7RT1488:16-1489:8.]

Rather than acknowledge this duty, the appellate court appears to have folded Janssen's clear misconduct into an inappropriate malpractice analysis, concluding

that "JRD's undertaking as the drug study sponsor cannot reasonably be construed to include a 'guarantee of safety' from any and all acts of medical malpractice by physicians who bear the primary responsibility for safeguarding the health of study participants." (*Id.*, at 19.) Thus, in contravention to federal law and clinical practice guidelines which require drug companies to independently monitor and protect the safety of study subjects, the appellate court concluded that drug companies are held entirely harmless from injury caused during drug trials, including affirmative acts of malfeasance.

Though the radical reformulation of duty contained in the Court of Appeal's Opinion is unpublished, the practical reality is that while unpublished decisions may not be cited as binding precedent, numerous courts have cited them in support of various analyses (see Eisenberg, *et al.*, *California Practice Guide: Civil Appeals and Writs* (Rutter 2017) ¶¶11:186.5-11:186.13), and one court even acknowledged that unpublished and depublished California cases could be discussed, so long as they are not actually "relied on" as precedent. (*Conrad v. Ball Corp.* (1994) 24 Cal.App.4th 439, 444 ["The message from the Supreme Court seems to be that unpublished opinions may be cited *if they are not 'relied on*'"].) And even respected practice guides like the Rutter Group's confirm that while unpublished decisions may not be cited as precedent, "counsel are free to use the *reasoning* in an unpublished opinion." (Eisenberg, at ¶ 11:186.13.) Thus, the appellate court's decision in this case will have continuing impact despite the fact that it is not published.[1]

1. This decision has already been widely disseminated on the internet. See

Appendix A

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CONCLUSION

Because of the critical importance of these issues with respect to the on-going risks to numerous Californians from the conduct of clinical trials, review of should be granted.

Dated: February 13, 2018

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/s/_____
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APPENDIX B — EXCERPTS OF CROSS-RESPONDENT'S BRIEF IN THE COURT OF APPEAL OF THE STATE OF CALIFORNIA, SECOND APPELLATE DISTRICT, DIVISION 5, DATED FEBRUARY 6, 2017

COURT OF APPEAL, STATE OF CALIFORNIA
SECOND APPELLATE DISTRICT, DIVISION 5

B269318/B270332

MARION LIU, AS THE SUCCESSOR IN INTEREST TO AUGUSTINE LIU, SR., DECEASED AND MARION LIU, INDIVIDUALLY AND AS SUCCESSOR IN INTEREST TO AUGSTINE LIU, II, DECEASED,

Plaintiff and Appellant,

vs.

JANSSEN RESEARCH & DEVELOPMENT, LLC,

Defendant and Respondent.

Appeal from Orders and Judgment of
the Superior Court of California,
County of Los Angeles, Case No. BC432254
The Hon. Richard Fruin, Judge Presiding

CROSS-RESPONDENT'S BRIEF OF MARION LIU

[TABLES INTENTIONALLY OMITTED]

Appendix B

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Similarly, Janssen's claim that it had only "remote" involvement or control over the conduct of the study does not survive scrutiny. Rather, as the testimony at trial confirmed, based on applicable regulations and guidelines, as the sponsor of the study, Janssen had the *ultimate* responsibility to monitor the study's day-to-day operation and to take action when the health or safety of a subject is compromised. [3RT571:14-578:9;653:6-656:8;4RT794:19-796:22;798:3-11;8RT1756:22-1759:2;1756:22-1759:2;1790:3-1798:4,1888:7-1889:2,1893:8-1894:10;4RT898:26-899:-7,900:17-903:10;10RT2156:20-2157:25;2159: 21-2161;10; 6RT1316:27-1318:24.] (21 C.F.R. § 312.50 [sponsor responsible for "ensuring proper *monitoring* of the investigation [and] ensuring that the investigation is conducted in accordance with the general investigational plan and protocols."][3]

That monitoring duty is an active one. (21 C.F.R. § 312.56(a) ["The sponsor shall monitor the progress of

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approval processes. [3RT540:22-26,545:10-557:26,549:4-550:556:5, 557:16-558:27,558:28-560:14,560:25-561:23.] von Schwartz, M.D. is triple Board Certified-Internal Medicine, Cardiology, Advanced Heart Failure [6RT1282:27-1283:5];Professor at Cedars and UCLA, Medical Director at various hospitals [6RT1283:20-1284:15];wrote book chapters on cardiomyopathy [6RT1295:1-7] and has conducted clinical trials. [6RT1236-1237.] Pitchon and Goodman are also well qualified. [6RT1177:5-1181:25;1184:25-1184:26;1185:23-1189:5; 9AA 1833:7-1834:24.]

3. All emphasis is added, and internal quotations and brackets are omitted.

all clinical investigations."].) Subdivision (b) requires that a "sponsor who discovers that an investigator is not complying with the signed agreement . . ., the general investigation plan, or the requirements of this part or other applicable parts *shall promptly either secure compliance or . . . end the investigator's participation in the investigation*."

That monitoring duty was also required by the Good Clinical Practice ("GCP") requirements imposed on Janssen, which identifies the purpose of monitoring: To assure that the "rights and well-being of human subjects is protected." [13AA2825,§5.18.1(a).] Specific monitoring functions include verifying that the investigators are complying with the protocol, "[*v]erifying* that the investigator is enrolling only eligible subjects" [13AA2827,§5.18.4(h),(i)] and taking action when non-compliance occurs. [13AA2830,§5.20;3RT575:7-577:15.]

As the Supreme Court explained more than 150 years ago, with power comes responsibility: "The responsibility is placed where the power exists. Having power to control, the superior or master is bound to exercise it to the prevention of injuries to third parties, or he will be held

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who lived in the home," and therefore owed a duty to protect them. (*Ibid.*)

The same is true here because a "reasonably thoughtful" drug study sponsor "would take into account

the possibility that" a study subject could suffer a deterioration in their health during the course of the study and need medical intervention. Indeed, the foreseeability of such a situation is actually confirmed in Janssen's own protocol, which provides that a study subject will be withdrawn from the study if necessary "for safety reasons." [10AA2236,¶4.5.2.]

The *Kesner* court also looked to government regulations and industry standards in assessing foreseeability, concluding that, in that case, those considerations also supported a conclusion that no categorical exception to the existence of a general duty applied. (*Kesner*, at 292-293.) The same is true here:

- Federal regulations impose express and specific responsibilities and requirements on study sponsors: "Sponsors are responsible for . . . ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols." (21 CFR § 312.50.) The sponsor is also expressly required to "*monitor the progress* of all clinical investigations" and "review and evaluate the evidence relating to the safety . . . . of the drug." (21 C.F.R. § 312.56.)

- The study protocol specifically provides that the study is to be performed pursuant to the provisions of the International Clinical Harmonization ("ICH") guidelines on Good Clinical Practices. [10AA2260,11.2.1.] Those guidelines, in turn, expressly delineate the responsibilities of both

> the sponsor and the investigator. Subsection 5.1.1 specifically imposes responsibility on the sponsor for "implementing and maintaining quality assurance and quality control systems with written SOPs [*i.e.*, standard operating procedures] to ensure that trials are conducted . . . in compliance with the protocol, GCP, and the applicable regulatory requirements." [13AA2817.]
>
> • One of Janssen's specific responsibilities included sufficient monitoring to assure that the "rights and well-being of human subjects are protected." [13AA2825,§5.18.1(a) Those monitoring responsibilities also specifically required Janssen to ensure that the trial was conducted and documented properly, that the investigational products are supplied only to subjects who are
>
> ***

of care rule would impose liability that was too broad, while establishing the standard of care by judicial fiat would be inappropriate in light of the need to conduct relevant inquiries, the appropriate course – in that particular context – was to employ the FDA standard as the standard of care. (*Id.*, at 553, 555.)

The circumstance in *Ramirez* was unique and the court emphasized the importance of applying the "standard" rule that regulations establish the *minimum* standard of care, not the *maximum* in most cases. (*Id.*, at 547-548.) And that standard rule applies in this case

because the regulations at issue themselves emphasize the importance of the sponsor's role in protecting the health and well- being of study subjects. (See, e.g., 21 C.F.R. §§ 312.50, 312.56(a); GCP§5.18(a).) Because the health and well-being of the subjects in a clinical study is of overriding importance, and because the regulations themselves expressly impose primary responsibility for the health and well-being of study subjects on the sponsor (*ibid.*), those mandates cannot be adequately implemented to protect study subjects unless common law notions of what constitutes reasonable conduct in the circumstances is the standard.

Furthermore, the FDA regulations do not provide detailed, minute-by-minute requirements for *how* the sponsor is to monitor the study, just that it must do so and, in doing so, must protect the subject. (21 C.F.R. 312.50.) Clearly, the FDA thought it appropriate to permit state law to fill in those details based on what is reasonable in light of the specific circumstances at issue, i.e., type of study, the type of subjects, the risks and the benefits. [13AA2825-2827,§5.18.3.].

And imposing ultimate liability on the sponsor, rather than permitting the sponsor to slough its obligations off onto the investigator is wholly consistent with Civil Code section 1714(a) and *Kesner*, as discussed above. Any other rule would encourage clinical trial sponsors to abdicate their responsibility for the protection of subjects in clinical trials intended to benefit their own financial interests, just as Janssen did here. If sponsors can simply lay off all responsibility onto the principal investigators, clinical

trial subjects will be ever more at risk from cost-cutting and cost-saving efforts by investigators attempting to maximize their own profits at the risk of participants' safety.

There is another reason to hold sponsors ultimately responsible for adverse consequences that occur during a drug trial: The sponsor knows more about the drug, and its risks and dangers, than the principal investigator or anyone else. Given the vastness of its own knowledge, the sponsor is in the best position to monitor and review the progress of

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5.
SINCE JANSSEN HAS NOT DEMONSTRATED THE EXISTENCE OF ANY EVIDENTIARY ERRORS OR MISCONDUCT, THERE IS NO BASIS FOR ASSERTING THAT CUMULATIVE ERROR WARRANTS REVERSAL

In its final argument Janssen asserts that *cumulative* error supports reversal. (OB59-63) Since Janssen never adequately demonstrated the existence of any error – or *prejudice* from any errors – no accumulation of such unsubstantiated "errors" support reversal. (*In re Reno* (2012) 55 Cal.4th 428, 483.)

Rather, Janssen's cumulative failures to comport with the established appellate review standards preclude reversal.

Appendix B

Dated: February 6, 2017

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