DURECT Corporation Announces Publication of DUR-928's Mechanism of Action

— DUR-928 is an inhibitor of DNA methyltransferases (DNMTs) regulating expression of genes involved in cell survival, inflammation and lipid biosynthesis

— Mechanism of action supports development of DUR-928 for the treatment of multiple acute organ injury and chronic diseases

— Published in peer reviewed Journal of Lipid Research

CUPERTINO, Calif., March 9, 2021 /PRNewswire/ — DURECT Corporation (Nasdaq: DRRX) today announced the publication of a peer-reviewed research paper describing the binding sites and proposed mechanism of action of its lead drug candidate, an endogenous sulfated oxysterol and epigenetic regulator, DUR-928, in The Journal of Lipid Research.

DUR-928 is an endogenous sulfated oxysterol that acts as an epigenetic regulator, a compound that regulates patterns of gene expression without modifying the DNA sequence. The publication shows that DUR-928 (referred to in the paper as 25HC3S) binds to and inhibits the activity of DNA methyltransferases (DNMTs), *DNMT-1, 3a and 3b*, epigenetic regulating enzymes that add methyl groups to DNA (a process called DNA methylation). As such, by inhibiting DNMT activity, DUR-928 inhibits DNA methylation, thereby regulating the expression of genes that modulate crucial cellular activities, including those associated with cell death, stress response, and lipid biosynthesis. These modulations may lead to improved cell survival, and reduced lipid accumulation and inflammation, as has been observed in various in vivo animal models and in results from DURECT's completed clinical trials in alcohol-associated hepatitis (AH) and non-alcoholic steatohepatitis (NASH).

"DNA hypermethylation, an example of epigenetic dysregulation, has been reported to be associated with certain diseases, like AH and NASH, a life-threatening acute liver disease characterized by lipid accumulation, severe inflammation and liver cell death, with an average 90-day mortality rate of 29%," said Norman Sussman, MD, FAASLD, Chief Medical Officer of DURECT. "DUR-928 has already demonstrated promising efficacy signals in a Phase 2a study in patients with AH and encouraging data in a Phase 1b study in patients with NASH. The proposed mechanism of action of DUR-928 in this publication provides a further scientific rationale for evaluating DUR-928 as a therapeutic agent for AH and NASH."

James E. Brown, D.V.M., President and Chief Executive Officer of DURECT, added, "We are focused on progressing our ongoing Phase 2b trial of DUR-928 in AH (AHFIRM), and in parallel, exploring additional indications that could benefit from DUR-928's mechanism of action."

In a Phase 2a clinical trial in patients with AH, 100% of patients treated with DUR-928 survived the 28-day follow-up period compared to a 26% historical average 28-day mortality rate. 74% of patients treated with DUR-928 were discharged within 4 days or less of treatment after one dose. In a Phase 1b trial, patients with NASH treated with DUR-928 experienced significant improvements in biomarkers of liver function and liver health, including liver enzymes and serum lipid profiles. A reduction in liver fat of more than 10% was observed in 43% of these patients.

The publication, entitled, "25-hydroxycholesterol 3-sulfate is an endogenous ligand of DNA methyltransferases in hepatocytes" is available online here: **https://www.jlr.org/article/S0022-2275(21)00045-6/fulltext**

About DUR-928
DUR-928 is an endogenous sulfated oxysterol and an epigenetic regulator. Epigenetic regulators are compounds that regulate patterns of gene expression without modifying the DNA sequence. DNA hypermethylation (an example of epigenetic dysregulation), results in transcriptomic reprogramming and cellular dysfunction, and has been found to be associated with many acute (e.g. AH) or chronic diseases (e.g. NASH). As an inhibitor of DNA methyltransferases (DNMT1, DNMT3a and 3b), DUR-928 inhibits DNA methylation , which subsequently regulates expression of genes that are involved in cell signaling pathways associated with stress responses, cell death and survival, and lipid biosynthesis. This may ultimately lead to improved cell survival, reduced

inflammation, and decreased lipotoxicity. As an epigenetic regulator, the proposed mechanism of action provides further scientific rationale for developing DUR-928 for the treatment of multiple acute organ injury and certain chronic diseases.

About Epigenetic Regulation
Epigenetic regulation influences the expression of genes through the silencing or initiation of gene activity without modifying the DNA sequence. For instance, methylation of cytosine nucleotides in promoter regions of DNA, facilitated by DNA methyltransferases (DNMTs), will generally result in downregulation of gene expression, while demethylation results in upregulation. DNA methylation/demethylation can thus regulate the expression of relevant genes, especially clusters of master genes that further modulate crucial cellular activities.

About DURECT Corporation
DURECT is a biopharmaceutical company committed to transforming the treatment of acute organ injury and chronic liver diseases by advancing novel and potentially lifesaving therapies based on its endogenous epigenetic regulator program. DUR-928, the company's lead drug candidate is in clinical development for the potential treatment of alcohol-associated hepatitis (AH) for which FDA has granted a Fast Track Designation. Non-alcoholic steatohepatitis (NASH) is also being explored. In addition, POSIMIR® (bupivacaine solution) for infiltration use, a non-opioid analgesic utilizing the innovative SABER® platform technology, is now FDA-approved. Full prescribing information about POSIMIR, including the Boxed Warning, can be found at www.posimir.com. For more information about DURECT, please visit www.www.durect.com and follow us on Twitter https://twitter.com/DURECTCorp.

DURECT Forward-Looking Statement
The statements in this press release regarding the potential for DUR-928 to treat patients with AH, NASH, and other diseases, multiple acute organ injury, ongoing and planned clinical trials of DUR-928, and the commercial potential of POSIMIR are forward-looking statements involving risks and uncertainties that can cause actual results to differ materially from those in such forward-looking statements. Potential risks and uncertainties include, but are not limited to, the risks that the clinical trial of DUR-928 in AH takes longer to conduct than anticipated due to COVID-19 or other factors, the risk that clinical trials of DUR-928 do not confirm the results from earlier clinical or pre-clinical trials, or do not demonstrate the safety or efficacy or the life saving potential of DUR-928 in a statistically significant manner, risks that we or a third-party licensee may not commercialize POSIMIR successfully, if at all, and risks related to our ability to obtain capital to fund operations and expenses. Further information regarding these and other risks is included in DURECT's Form 10-K filed on March 5, 2021 under the heading "Risk Factors."

NOTE: POSIMIR® and SABER® are trademarks of DURECT Corporation. Other referenced trademarks belong to their respective owners. DUR-928 is an investigational drug candidate under development and has not been approved for commercialization by the U.S. Food and Drug Administration or other health authorities for any indication. Full prescribing information for POSIMIR, including its Boxed Warning, can be found at www.posimir.com.

View original content:http://www.prnewswire.com/news-releases/durect-corporation-announces-publication-of-dur-928s-mechanism-of-action-301243414.html

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