DURECT Corporation Presents Additional Clinical Data from DUR-928 Phase 1b Trial in NASH and Phase 1 Trial in Hepatic Impairment at the International Liver Conference 2021 (EASL)

New Data Further Supports DUR-928's Potential in Acute and Chronic as well as Moderate and Severe Liver Disease

CUPERTINO, Calif., June 23, 2021 /PRNewswire/ — DURECT Corporation (Nasdaq: DRRX) today announced the presentation of additional clinical data from a DUR-928 Phase 1b trial in non-alcoholic steatohepatitis (NASH) and a Phase 1 trial in subjects with hepatic impairment (HI) as part of two posters at the 2021 International Liver Conference (EASL) being held virtually June 23-26, 2021.

"We are pleased to report additional signals of potential efficacy from our Phase 1b NASH trial of DUR-928, our lead epigenetic regulator," said James E. Brown, D.V.M., President and CEO of DURECT. "The roughly 20% median reduction from baseline of HOMA-IR, an important indicator of insulin resistance, observed after only 4 weeks of daily oral administration at the 50 mg and 150 mg dose levels, is similar to the level of reductions seen in longer term studies of several well-established diabetes therapeutics. In addition, the Phase 1 trial in subjects with moderate and severe hepatic function impairment further demonstrates DUR-928's safety and potential efficacy profile in subjects with serious liver disease. We continue to make progress opening new clinical trial sites and enrolling patients in our ongoing AHFIRM Phase 2b trial in alcohol-associated hepatitis (AH) patients while we determine next steps for DUR-928 in NASH and explore additional potential acute and chronic indications."

Poster #1198 entitled "Efficacy Signals of 4-Week Oral DUR-928 in NASH Subjects," presented by Eric Lawitz, M.D., Vice President, Scientific and Research Development, Texas Liver Institute, disclosed additional potential efficacy signals from DURECT's Phase 1b clinical study of orally administered DUR-928 in nonalcoholic steatohepatitis (NASH) patients. Key highlights include:

- **Improvement from baseline in insulin resistance** as assessed by the homeostatic model assessment (HOMA-IR). Subjects in the 50 mg and 150 mg groups had 22% and 18% median reductions (not statistically significant) of HOMA-IR from baseline respectively after 4 weeks of daily oral dosing of DUR-928. Subjects in the 600 mg group did not show a change in HOMA-IR.
- **Improvement from baseline in liver stiffness**, assessed by transient elastography (TE), magnetic resonance elastography (MRE) and the liver fibrosis marker pro-C3.
- Previously reported data showed improvement from baseline in: **liver enzymes** such as ALT, AST and GGT and improvements in serum lipid profiles such as LDL-C, non-HDLC and triglycerides; **liver fat** by MRI-PDFF imaging; and **biomarkers of liver health**, such as CK-18, a cell death biomarker, certain of which were statistically significant improvements.
- **Safety profile:** DUR-928 was safe and well tolerated by all subjects in the study.

Data highlights from Poster #668 entitled "Safety and Pharmacokinetics of DUR-928 in Hepatic Function Impaired Subjects," presented by Jaymin Shah, Ph.D., Executive Director, Clinical Pharmacology and Pharmacokinetics at DURECT, included:

- **Safety profile:** DUR-928 was safe and well-tolerated by all moderate and severe hepatic impairment (HI) subjects with no adverse events and no dose-limiting toxicity reported throughout the study.
- **Pharmacokinetics:** As expected, clearance of DUR-928 was decreased in HI subjects compared to matched control subjects with normal hepatic function, leading to a 4-10 fold higher drug exposure (Cmax and AUC) in HI subjects depending on the severity of HI.
- **Initial efficacy signals:** A single oral dose of 200 mg of DUR-928 in subjects with HI resulted in statistically significant

median reductions from baseline of the apoptosis biomarker M30 (cCK-18) at 12 hours post-dose.

Copies of the posters will be available on DURECT's corporate website here at the conclusion of the conference.

About the DUR-928 NASH Phase 1b Trial
The Phase 1b study was a randomized, open-label, multi-center U.S. study to evaluate safety, pharmacokinetics and signals of biological activity of DUR-928 in NASH subjects with stage 1-3 fibrosis. A total of 65 patients completed the study. DUR-928 was orally administered daily at 50 mg (n=23), 150 mg (n=21), or 600 mg (300 mg BID (n=21)) for 4 weeks and followed up for an additional 4 weeks.

About the DUR-928 Phase 1 Trial in Hepatic Liver Impairment
The Phase 1 study was an open-label, multi-center U.S. study to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of DUR-928 in subjects with moderate (Child-Pugh B scores) and severe (Child-Pugh C scores) hepatic impairment, who received a single oral dose of 200 mg DUR-928.

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 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 generally 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. The Company is conducting a double-blind, placebo-controlled Phase 2b clinical trial called AHFIRM, evaluating DUR-928's lifesaving potential compared to the current standard of care in patients with severe AH. 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, HI and other diseases, such as acute organ injury, its potential to reduce HOMA-IR, 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 (AHFIRM) takes longer to conduct than anticipated due to COVID-19 or other factors, the risk that clinical trials of DUR-928, including AHFIRM, do not confirm the results from earlier clinical or pre-clinical trials, or do not demonstrate the safety or efficacy or the lifesaving 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-Q filed on May 5, 2021 under the heading "Risk Factors."

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-presents-additional-clinical-data-from-dur-928-phase-1b-trial-in-nash-and-phase-1-trial-in-hepatic-impairment-at-the-international-liver-conference-2021-easl-301318390.html

SOURCE DURECT Corporation

Corporate Contact, Mike Arenberg, DURECT, Chief Financial Officer, +1-408-346-1052, mike.arenberg@durect.com; Media Contact, Mónica Rouco Molina, Ph.D., LifeSci Communications, +1-929-469-3850, mroucomolina@lifescicomms.com