DURECT Corporation Announces Update on DUR-928 Development Program

Initial data from Phase 1b study in NASH

CUPERTINO, Calif., Oct. 31, 2016 /PRNewswire/ — DURECT Corporation (Nasdaq: DRRX) today provided an update on the DUR-928 development program including a description of data from the first cohort of a Phase 1b study with DUR-928 in patients with nonalcoholic steatohepatitis (NASH).

“We are pleased to report data from cohort one of the first patient study with DUR-928, and that a single dose provided signals of DUR-928 activity in cirrhotic and non-cirrhotic NASH patients,” stated James E. Brown, D.V.M., President and CEO of DURECT. “These recent DUR-928 data in patients are consistent with DUR-928 activities previously demonstrated in animal models and in cell cultures. Additionally, we are reporting on two new animal studies that are suggestive of DUR-928’s potential therapeutic activities in fibrotic and cholestatic liver diseases, and are preparing two IND’s to enable future clinical trials in the U.S.”

“I recently reviewed data from the Phase 1b trial and am impressed to see this kind of signal with just a single dose,” stated Arun Sanyal, M.D., Professor of Medicine Physiology and Molecular Pathology at Virginia Commonwealth University, and a past President of the American Association for the Study of Liver Diseases (AASLD).

Update on the Epigenetic Regulator Program

DUR-928, our Epigenetic Regulator Program’s lead product candidate, is an endogenous, small molecule, new chemical entity (NCE), which may have broad applicability in several metabolic diseases such as nonalcoholic steatohepatitis (NASH), and in acute organ injuries such as acute kidney injury.

Phase 1b trial in patients with NASH

Our first patient trial utilizing DUR-928 is an open-label, single-ascending-dose safety and pharmacokinetic (PK) Phase 1b trial in liver function impaired (NASH) patients and matched control subjects (matched by age, body mass index and gender with normal liver function). This study is being conducted in successive cohorts evaluating single-dose levels of orally administered DUR-928. The first, low dose, cohort consisted of 10 subjects with NASH (of which 4 were cirrhotic and 6 were not cirrhotic) and 6 matched control subjects. After a PK/safety review of this cohort, the study has proceeded to the higher dose cohort utilizing a dose four times larger than the low dose cohort. Data from the first cohort showed the PK parameters between the NASH patients and the matched control subjects were comparable.

While this study was not designed to assess the efficacy of DUR-928 as a therapy for NASH, certain clinical chemistry biomarkers for liver function and liver injury were reduced 12 hours after dosing with DUR-928 as compared to before dosing. Furthermore, high sensitivity C-Reactive Protein (hsCRP), a marker of inflammation, was reduced after dosing with DUR-928. IL-18, an inflammatory mediator implicated in both liver and kidney diseases, decreased in the NASH patients as soon as a few hours after dosing, with the effect more pronounced in cirrhotic subjects at 12 hours after dosing; there was little or no change of IL-18 levels in matched control subjects. In addition, both full length CK18 (a generalized cell death marker) and cleaved CK18 (a cell apoptosis marker) were reduced after DUR-928 treatment in the NASH patients, with the effect more pronounced in cirrhotic subjects, and little or no change in matched control subjects. Collectively, the reduction of these biomarkers plus results from our animal and cell culture studies suggest potential therapeutic activity of DUR-928 for patients with liver disease. However, additional studies are required to evaluate the safety and efficacy of DUR-928, and there is no assurance that these biomarker effects will be observed in a statistically significant manner, or that DUR-928 will demonstrate safety or efficacy in treating NASH or other liver diseases, in larger controlled trials.

We are currently enrolling and dosing patients in the higher dose cohort, which we expect to complete in 2016, and we expect that this single-ascending-dose Phase 1b trial will enable and inform future studies in patients with liver diseases. We have also recently requested a pre-IND meeting with the U.S. Food and Drug Administration (FDA) as precursor to submitting an IND, which is required to enable a future liver disease clinical trial in the United States.

Phase 1b trial in patients with impaired kidney function

Our second Phase 1b study with DUR-928, also being conducted in Australia, is an open-label, single-ascending-dose safety and pharmacokinetic study in patients with impaired kidney function (stage 3 and 4 chronic kidney disease) and matched control subjects with normal kidney function. After a PK/safety review of the low dose, the study may proceed to a higher dose. Assuming both cohorts are dosed, the study will comprise approximately 16-18 subjects, of which approximately 10-12 will have received DUR-928. We anticipate that we will obtain results from this trial in 2016, and that this trial will enable and inform subsequent patient studies in acute kidney injury and/or other kidney diseases. We recently held a pre-IND meeting with the Cardiovascular and Renal Products Division of the FDA; we anticipate utilizing feedback from that meeting as well as from our clinical advisors to file an IND which is required to enable a future kidney disease clinical trial in the United States.

Results from additional animal studies

Previously we communicated that the biological activity of DUR-928 has been demonstrated in 8 different animal disease models involving three animal species. These models represent acute organ injuries and chronic disorders involving kidney, liver, brain and multi-organ injuries. Today we are reporting on two additional animal disease models:

- A second study in a mouse model of advanced NASH (STAM model). In this model, conducted by a Contract Research Organization (CRO) in Japan, NASH is induced in diabetic mice fed a high fat diet. In a previously reported study with this model, the treatment with DUR-928 was initiated when fatty liver had formed and stopped after fibrosis developed. Daily oral administration of DUR-928 for 4 weeks resulted in inhibition of the progression of liver inflammation, hepatocyte ballooning and fibrosis. In this newer study, the treatment was initiated after fibrosis had formed and stopped after nodules had developed. Daily oral administration of DUR-928 for 4 weeks resulted in statistically significant reduction of fibrosis and hepatocyte ballooning as compared to placebo control. The fibrosis seen at the end of the study in DUR-928 treated animals was less than that seen at the beginning of the treatment. The hepatocyte ballooning seen at the end of the study in the DUR-928 group was significantly lower than at the beginning of the treatment.
- Bile duct ligation rat model (a model for cholestatic liver diseases such as Primary Sclerosing Cholangitis or PSC). In two studies, conducted by a CRO in Canada, the bile duct was surgically ligated, resulting in cholestatic inflammatory liver injury. Daily oral administration for nine days of DUR-928 showed significant improvement in body temperature and body weight, as well as a statistically significant reduction of total bilirubin (including both direct and indirect bilirubin).

Conference Call

These results will be discussed during a live audio webcast of a conference call to discuss third quarter 2016 results that will be broadcast live over the internet at 4:30 p.m. Eastern Time on October 31 and is available by accessing DURECT's homepage at www.www.durect.com and clicking "Investor Relations." If you are unable to participate during the live webcast, the call will be archived on DURECT's website under Audio Archive in the "Investor Relations" section.

About DURECT Corporation

DURECT is a biopharmaceutical company actively developing new therapeutics based on its Epigenetic Regulator Program and proprietary drug delivery platforms. DUR?928, a new chemical entity in Phase 1 development, is the lead candidate in DURECT's Epigenetic Regulator Program. An endogenous, orally bioavailable small molecule, DUR-928 has been shown in preclinical studies to play an important regulatory role in lipid homeostasis, inflammation, and cell survival. Human applications may include acute organ injury and chronic metabolic diseases such as nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). DURECT's advanced oral, injectable, and transdermal delivery technologies are designed to enable new indications and enhanced attributes for small-molecule and biologic drugs. One late-stage development program in this category is POSIMIR® (SABER®-Bupivacaine), an investigational analgesic product intended to address key unmet needs in postoperative pain management. Another is REMOXY® ER (oxycodone), an investigational new drug based on DURECT's ORADUR® technology. For more information, please visit www.www.durect.com.

NOTE: POSIMIR®, SABER®, and ORADUR® are trademarks of DURECT Corporation. Other referenced trademarks belong to their respective owners. REMOXY ER, POSIMIR, DUR-928 and ORADUR-Methylphenidate are drug candidates under development and have not been approved for commercialization by the U.S. Food and Drug Administration or other health authorities.

DURECT Forward-Looking Statement

The statements in this press release regarding the potential benefits and uses of our drug candidates, including the potential use of DUR-928 to treat NASH, other liver disease or kidney disease, the potential use of POSIMIR to treat pain, clinical trial plans for DUR-928 and potential markets for DUR-928 and 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 future clinical trials of DUR-928 do not demonstrate the safety or efficacy of DUR-928 in a statistically significant manner, that the PERSIST clinical trial of POSIMIR will take longer to conduct than anticipated or result in data that will not support a successful NDA resubmission or product approval, the risk of delays in the commencement, enrollment or completion of other clinical trials, the risk that prior clinical trials will not be confirmed in subsequent trials, the potential failure of clinical trials to meet their intended endpoints, the risk of adverse decisions by regulatory agencies or delays and additional costs due to requirements imposed by regulatory agencies, additional time and resources that may be required for development, testing and regulatory approval of DUR-928, potential adverse effects arising from the testing or use of our drug candidates, 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 August 2, 2016 under the heading "Risk Factors."

SOURCE DURECT Corporation

Matt Hogan, Chief Financial Officer, DURECT Corporation, 408-777-4936