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Aradigm Submits New Drug Application (NDA) to FDA for U.S. Marketing Approval of Linhaliq in Non-Cystic Fibrosis Bronchiectasis

HAYWARD, Calif.--(BUSINESS WIRE)-- **Aradigm Corporation (NASDAQ: ARDM)** (the "Company") today announced it has submitted its New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for Linhaliq™ for the treatment of non-cystic fibrosis bronchiectasis (NCFBE) patients with chronic lung infections with *Pseudomonas aeruginosa* (*P. aeruginosa*).

Pursuant to the Food and Drug Administration Modernization Act of 1997 (FDAMA) Sec. 115(a) and FDA guidance, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998), Aradigm is submitting the Linhaliq NDA based on the positive Phase 3 pivotal clinical trial ARD-3150-1202 (ORBIT-4) and confirmatory evidence from Phase 3 study ARD-3150-1201 (ORBIT-3) and Phase 2b study ARD-3150-0902 (ORBIT-2), together with other supporting evidence from proprietary preclinical and clinical studies, as well as referencing other information about ciprofloxacin from publicly available sources.

Aradigm received Orphan Drug Designation for liposomal ciprofloxacin for inhalation for the management of bronchiectasis and of Linhaliq for the management of bronchiectasis. Additionally, for Linhaliq, Aradigm was granted Qualified Infectious Disease Product (QIDP) Designation for the treatment of NCFBE patients with chronic lung infections with *P. aeruginosa* followed by Fast Track Designation.

The FDA has a 60-day filing review period to determine whether the NDA is complete and acceptable for filing.

Additional Information about Linhaliq Phase 3 Trials and Regulatory Development

Linhaliq, formerly known as Pulmaquin®, is composed of a mixture of liposome encapsulated and unencapsulated ciprofloxacin. Ciprofloxacin, available in oral and intravenous formulations, is a widely prescribed antibiotic. It is used often to treat acute lung infections because of its broad-spectrum antibacterial activity against various bacteria, such as *P. aeruginosa*. There are currently no treatments approved for NCFBE patients to prevent and reduce the number of pulmonary exacerbations (PEs).

Linhaliq was evaluated in two Phase 3 studies (ORBIT-3 and ORBIT-4) to determine its safety and effectiveness as a once-a-day inhaled formulation for the chronic treatment of patients with NCFBE who have chronic lung infections with *P. aeruginosa*.

The Phase 3 clinical program for Linhaliq in NCFBE consisted of two worldwide, double-blind, placebo-controlled pivotal trials (ORBIT-3 and ORBIT-4) that were identical in design except for a pharmacokinetics sub-study that was conducted in one of the trials. Each trial enrolled NCFBE patients (278 in ORBIT-3 and 304 in ORBIT-4) into a 48-week double-blind period consisting of 6 cycles of 28 days on treatment with Linhaliq or placebo plus 28 days off treatment, followed by a 28 day open label extension in which all participants received Linhaliq (total treatment duration, including the double-blind period, of approximately one year). The superiority of Linhaliq vs. placebo during the double-blind period was evaluated in terms of the primary endpoint - time to first PE, while key secondary endpoints included the reduction in the number of PEs and the number of severe PEs, and improvements in quality of life measures. Lung function was monitored as a safety indicator.

Aradigm discussed the results of the Phase 3 studies at meetings with FDA in December 2016 and March 2017. Based on these discussions, the statistical analysis of the results was changed from the pre-specified plan to stratification based on sex and the frequency of pulmonary exacerbations in the prior year, as the stratum for current smokers contained a small number of subjects.

Top-line results for the two Phase 3 studies using the new stratification are described below:

In ORBIT-4 the median time to first PE was 230 days in the Linhaliq treatment group as compared to 158 days in the placebo group. This increase of 72 days in the median time to first PE was statistically significant (p=0.0323) using stratified unweighted log-rank analysis. For the first secondary efficacy endpoint, there was a 37% reduction in the frequency of PEs over the 48-week treatment period in the Linhaliq treatment group as compared to the placebo group. This result was

statistically significant (p=0.0006). In the analysis of the second secondary endpoint, a statistically significant 60% reduction in the frequency of severe PEs in the Linhaliq group compared with placebo was found (p=0.0031).

In ORBIT-3 the median time to first PE was 214 days in the Linhaliq treatment group as compared to 136 days in the placebo group. This increase of 78 days in the median time to first PE was similar to ORBIT-4 but was not statistically significant (p=0.9743). For the first secondary efficacy endpoint, there was a 15% reduction in the frequency of PEs over the 48-week treatment period in the Linhaliq treatment group as compared to the placebo group but it was not statistically significant (p=0.2565). In the analysis of the second secondary endpoint, a statistically non-significant 20% reduction in the frequency of severe PEs in the Linhaliq group compared with placebo was found (p=0.4827).

In neither trial did Linhaliq compared to placebo demonstrate a statistically significant improvement in the third secondary endpoint of the quality of life using the difference in the Respiratory Domain score of the QoL-B questionnaire between baseline and Week 48.

Both studies demonstrated a statistically significant reduction in P. aeruginosa density at Day 28, the end of the first on-treatment period (ORBIT-3: p= < 0.0001; ORBIT-4: p= < 0.0001). For each study, the magnitude of this antibiotic effect remained persistent throughout all on-treatment periods. Similarly, the Phase 2b trial ORBIT-2 met its primary efficacy endpoint of reduction of P. aeruginosa density at Day 28 (p=0.002).

Linhaliq was generally safe and well tolerated in both Phase 3 studies. There were no significant differences in the changes of lung function (FEV1 % predicted and FVC % predicted) or symptoms of airway irritation between the Linhaliq and placebo groups in the two studies. Overall, the incidence of all treatment emergent adverse events ("TEAE") was similar between the Linhaliq and placebo groups in both ORBIT-3 (Linhaliq: 89.6%; placebo: 91.6%) and ORBIT-4 (Linhaliq: 86.9%; placebo: 96.9%). In ORBIT-3 the rates of serious TEAEs were 30.6% with Linhaliq and 25.3% with placebo while in ORBIT-4 the rates were 17.0% versus 28.6%.

For each Phase 3 study, the randomization rate of Linhaliq-treated subjects to placebo was 2 to 1. There were 8 deaths in ORBIT-3 (Linhaliq: 5 (2.7%); placebo: 3 (3.2%)) and 6 deaths in ORBIT-4 (Linhaliq: 2 (1.0%); placebo: 4 (4.1%)). None of the deaths was considered related to Linhaliq or placebo by the investigators. The most frequently observed treatment-related TEAEs were of respiratory/thoracic/mediastinal nature and were reported in ORBIT-3 by 25.7% of subjects with Linhaliq and in 21.1% of subjects with placebo, while the rates in ORBIT-4 were 16.5% with Linhaliq versus 20.4% with placebo. There were no deaths in ORBIT-2.

After the completion of the 48-week double-blind period of the Phase 3 studies, both Linhaliq and placebo treated patients were given the opportunity to receive Linhaliq in a 28-day open label extension period. Eighty-nine percent of the patients who completed ORBIT-3 and 91% percent of the patients who completed ORBIT-4 enrolled in the extension period.

Further information about the analyses of the Phase 3 results is presented at Aradigm's website www.aradigm.com.

In addition, Aradigm intends to submit Linhaliq for marketing authorization in the European Union for the treatment of patients with NCFBE who have chronic lung infections with *P. aeruginosa*.

About Non-Cystic Fibrosis Bronchiectasis

NCFBE is a severe, chronic and rare disease characterized by abnormal dilatation of the bronchi and bronchioles, frequently associated with chronic lung infections. It is often a consequence of a vicious cycle of inflammation, recurrent lung infections, and bronchial wall damage. NCFBE represents an unmet medical need with high morbidity and mortality that affects more than 150,000 people in the U.S. and over 200,000 people in Europe. There is currently no drug approved for the treatment of this condition. NCFBE patients who have chronic infections with *P. aeruginosa* have a 6.5-fold increase in hospitalization, three times higher mortality, and a worse quality of life compared with those without *P. aeruginosa* infections.

About Aradigm

Aradigm is an emerging specialty pharmaceutical company focused on the development and commercialization of drugs for the prevention and treatment of severe respiratory diseases. Aradigm has completed Phase 3 development of Linhaliq (an investigational proprietary formulation of ciprofloxacin for inhalation) for the treatment of NCFBE. Aradigm's inhaled ciprofloxacin formulations including Linhaliq are also product candidates for treatment of patients with cystic fibrosis and non-tuberculous mycobacteria, and for the prevention and treatment of high threat and bioterrorism infections, such as inhaled tularemia, pneumonic plague, melioidosis, Q fever and inhaled anthrax.

More information about Aradigm can be found at www.aradigm.com.

Forward-Looking Statements

Except for the historical information contained herein, this news release contains forward-looking statements that involve risk and uncertainties, including those related to the ability to continue successful product development of our potential product candidates, such as Linhaliq; risks associated with the process of developing, manufacturing and obtaining regulatory approval for drugs that are safe and effective for use as human therapeutics; our reliance on third parties to manufacture Linhaliq, which could delay or limit its future development or regulatory approval; our ability to meet anticipated regulatory approval and commercial launch dates for Linhaliq; the fact that we will require additional capital to support the US and EU regulatory process for Linhaliq or any other product candidates, and may be unable to obtain such additional capital in sufficient amounts or on terms acceptable to us; the risk that we may not be able to maintain and enforce our intellectual property, including intellectual property related to Linhaliq; regulatory developments and safety issues, including difficulties or delays in obtaining regulatory approvals to market Linhaliq; the risk that the FDA and foreign regulatory authorities may not agree with our interpretation of the data from our clinical trials of Linhaliq and may require us to conduct additional clinical trials; Linhaliq may not receive regulatory approval or be successfully commercialized, including as a result of the FDA's or other regulatory authorities' decisions regarding labeling and other matters that could affect its availability or commercial potential; risks related to key employees, markets, economic conditions, health care reform, prices and reimbursement rates, as well as the other risks detailed from time to time in the Company's filings with the Securities and Exchange Commission (SEC), including the Company's Annual Report on Form 10-K for the year ended December 31, 2016 filed with the SEC on March 30, 2017, and the Company's Quarterly Reports on Form 10-Q.

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