# Immunic, Inc. Announces FDA Clearance to Begin IMU-838 Phase 3 ENSURE Studies in Relapsing-Remitting Multiple Sclerosis and Phase 2 CALLIPER Study in Progressive Multiple Sclerosis

*– Phase 3 ENSURE Program in Relapsing-Remitting Multiple Sclerosis (RRMS) Comprises Twin Studies Evaluating Efficacy, Safety, and Tolerability of IMU-838 Versus Placebo, Intended to Provide Straightforward Path to Regulatory Approval –*

*– Supportive Phase 2 CALLIPER Trial in Progressive Multiple Sclerosis (PMS), Designed to Corroborate IMU-838's Neuroprotective Potential and Support Differentiated Profile –*

*– Company Expects Initiation of Both ENSURE and CALLIPER in the Second Half of 2021 –*

*– Conference Call and Webcast to be Held July 1, 2021 at 8:00 am ET –*

**NEW YORK, July 1, 2021 – Immunic, Inc. (Nasdaq: IMUX),** a clinical-stage biopharmaceutical company focused on developing best-in-class, oral therapies for the treatment of chronic inflammatory and autoimmune diseases, today announced U.S. Food and Drug Administration (FDA) clearance of its Investigational New Drug (IND) application for the phase 3 ENSURE program of lead asset IMU-838, the company's selective oral DHODH inhibitor, in patients with relapsing-remitting multiple sclerosis (RRMS). In addition, the FDA also cleared the company's separate IND application for the supportive phase 2 CALLIPER trial of IMU-838 in patients with progressive multiple sclerosis (PMS).

The ENSURE program comprises two multicenter, randomized, double-blind phase 3 trials designed to evaluate the efficacy, safety, and tolerability of IMU-838 versus placebo in RRMS patients. Based on IMU-838's robust activity in preventing lesion formation in the company's phase 2 EMPhASIS trial in RRMS, the strong and consistent correlation observed between lesion formation and clinical relapse in third-party clinical trials, and the drug's robust safety profile to date, Immunic believes that this phase 3 program provides a simple and straightforward path towards potential regulatory approval of IMU-838 in RRMS.

The multicenter, randomized, double-blind, placebo-controlled phase 2 CALLIPER trial is intended to run concurrently with and to complement the phase 3 program in RRMS. In particular, CALLIPER is focused on progressive forms of multiple sclerosis (MS) and designed to corroborate IMU-838's neuroprotective potential, as exemplified by slowing of brain atrophy and delay in disability worsening. Neurodegeneration is a key concern in both PMS and RRMS, since axonal and neural damage is responsible for the increasing and often severe disability experienced by patients. Immunic believes that, if the CALLIPER trial is successful in showing a beneficial effect of IMU-838, this data, along with the ENSURE program and IMU-838's strong safety and tolerability profile, may allow for a meaningful clinical differentiation of IMU-838 from other oral MS medications and an attractive commercial positioning. Although a supportive trial, Immunic does not believe that data from the CALLIPER trial are a pre-condition for filing a New Drug Application in RRMS.

"IMU-838's phase 2 results in relapsing-remitting multiple sclerosis showed an encouraging balance between efficacy, safety, and tolerability and I look forward to the phase 3 program in this indication," commented **Robert J. Fox, M.D., Staff Neurologist, Mellen Center for Multiple Sclerosis, Vice-Chair for**

**Research, Neurologic Institute, Cleveland Clinic, Cleveland, Ohio, and Coordinating Investigator of the ENSURE and CALLIPER programs.** "Disability progression is a principal concern for clinicians and patients of both PMS and RRMS. The ongoing disability worsening, even in periods without relapse, not only diminishes quality-of-life but can also ultimately lead to profound impairments in patient mobility. There is a clear unmet need for new therapeutic options which can help delay or arrest this process and I look forward to seeing data on IMU-838's neuroprotective potential." Dr. Fox receives compensation as a chair of the steering committees for the ENSURE and CALLIPER programs.

"IND clearance for our phase 3 program in RRMS is yet another seminal moment for Immunic as it progresses our lead asset, IMU-838, into a pivotal program and heralds the final phase of clinical development in MS. We believe that the phase 3 ENSURE program meaningfully simplifies IMU-838's regulatory approval path in MS as it applies a very clean and straightforward study design," stated **Daniel Vitt, Ph.D., Chief Executive Officer and President of Immunic**. "In addition, together with our MS expert panel, we designed the CALLIPER trial to study patients who currently are not typically treated with relapse preventing therapies. Our goal is to highlight IMU-838 as a therapy that combines truly differentiated safety and tolerability with neuroprotective activity such as slowing of brain atrophy and disability worsening. In our view, success in the CALLIPER trial could provide an important differentiator for IMU-838 in the MS market. We look forward to hopefully providing IMU-838 as an important new therapeutic option to MS patients within the next few years."

Each of the identical twin phase 3 trials, titled ENSURE-1 and ENSURE-2, is expected to enroll approximately 1,050 adult patients with active RMS at more than 100 sites in 14 countries, including the United States, Latin America, Central and Eastern Europe, and India. Patients will be randomized in a double-blinded fashion to either 30 mg daily doses of IMU-838 or placebo and the primary endpoint for both trials is time to first relapse up to 72 weeks. Key secondary endpoints include volume of new T2-lesions, time to confirmed disability progression, time to sustained clinically relevant changes in cognition, and percentage of whole brain volume change, grey matter volume, and white matter volume. With regard to the disability progression endpoint, the ENSURE program applies a pooled analysis of disability worsening across both trials, which may be further supported by data from the CALLIPER trial.

The ENSURE trials will be run concurrently, with dosing of the first patient expected in the second half of 2021. An interim analysis to assess event rates is planned to occur after a certain number of relapses have occurred in the double-blind treatment periods. This analysis is intended to inform potential sample size adjustment and help ensure that final study readout is not planned to occur before sufficient events have been achieved. This interim analysis is not intended as a futility analysis.

The phase 2 CALLIPER trial is expected to enroll approximately 450 patients at more than 70 sites in North America, Western, Central and Eastern Europe with patients randomized to either 45 mg daily doses of IMU-838 or placebo in a double-blinded fashion. The trial's primary endpoint is the annualized rate of percent brain volume change up to 120 weeks. Key secondary endpoints include the annualized rate of change in whole brain atrophy and time to 24-week confirmed disability progression based on the expanded disability status scale (EDSS). Dosing of the first patient is expected in the third quarter of 2021.

An interim analysis comprising an unblinded analysis of serum neurofilament light chain (NfL) is planned to occur once approximately half of the enrolled patients have completed 24 weeks of treatment. NfL has been shown consistently to correlate with disease activity in neurological disorders and has become one of the most important serum biomarkers for axonal damage over the past few years. As previously

reported, results of the phase 2 EMPhASIS trial of IMU-838 in RRMS showed a robust decrease in serum NfL at 24 weeks (-17.0% for 30 mg and -20.5% for 45 mg), as compared to baseline values, while the patients on placebo experienced a 6.5% increase in serum NfL over the same period.

"The Immunic team is very excited to see IMU-838 progressing into a pivotal program in RRMS. Based on its very strong safety and tolerability profile along with its robust efficacy, which we are planning to further highlight with neuroprotective data from the CALLIPER trial, we believe that IMU-838 has the potential to become a well-differentiated new treatment option for MS patients," added **Andreas Muehler, M.D., Chief Medical Officer of Immunic**. "In our discussions with regulatory authorities, including the FDA and the European Medicines Agency, testing IMU-838 against placebo was viewed as a reasonable approach for our phase 3 program, from both a regulatory and scientific perspective, as placebo provides the cleanest comparator to show proof-of-efficacy and to underline IMU-838's existing safety and tolerability profile."

**Conference Call and Webcast Information**

Immunic's management team will host a public conference call and webcast on July 1, 2021 at 8:00 a.m. Eastern Time to discuss the company's overall MS development strategy, the phase 3 ENSURE program in RRMS, and the phase 2 CALLIPER trial in PMS.

To participate in the conference call, dial 1-877-870-4263 (USA) or 1-412-317-0790 (International) and ask to be joined into the Immunic, Inc. call. A live, listen-only webcast of the conference call can be accessed at https://www.webcaster4.com/Webcast/Page/2301/39951 or on the "Events and Presentations" section of Immunic's website at ir.imux.com/events-and-presentations.

An archived replay of conference call and webcast will be available approximately one hour after the completion for one year on Immunic's website at: ir.imux.com.

**About Multiple Sclerosis**

Multiple sclerosis (MS) is an autoimmune disease that affects the brain, spinal cord and optic nerve. In MS, myelin, the coating that protects the nerves, is attacked and damaged by the immune system. Thus, MS is considered an immune-mediated demyelinating disease of the central nervous system. MS affects approximately one million people in the United States, and more than 2.8 million people worldwide. The disease mainly affects young adults of prime working age, although MS can occur at any age. MS is at least two to three times more common in women than in men.

Relapsing-remitting MS (RRMS) is the most common form of the disease. Approximately 85% of patients with MS are expected to develop RRMS, with some of these patients later developing more progressive forms of the disease. RRMS is characterized by clearly defined attacks of new or increasing neurologic symptoms. These relapses are followed by periods of remission, or partial or complete recovery. During remissions, all symptoms may disappear, or some symptoms may continue and become permanent. MS is a progressive disease which, without effective treatment, leads to severe disability.

Progressive MS (PMS) includes both primary progressive MS (PPMS) and secondary progressive MS (SPMS). PPMS is characterized by steadily worsening neurologic function from the onset of symptoms

without initial relapse or remissions. SPMS is identified following an initial relapsing remitting course, after which the disease becomes more steadily progressive, with or without other disease activity present.

**About IMU-838**

IMU-838 is an orally available, next-generation selective immune modulator that inhibits the intracellular metabolism of activated immune cells by blocking the enzyme dihydroorotate dehydrogenase (DHODH). IMU-838 acts on activated T and B cells while leaving other immune cells largely unaffected and allows the immune system to stay functioning, e.g. in fighting infections. In previous trials, IMU-838 did not show an increased rate of infections compared to placebo. In addition, DHODH inhibitors, such as IMU-838, are known to possess a host-based antiviral effect, which is independent with respect to specific virus proteins and their structure. Therefore, DHODH inhibition may be broadly applicable against multiple viruses. IMU-838 was successfully tested in two phase 1 clinical trials in 2017 and is currently being tested in a phase 2 trial in patients with ulcerative colitis. In the third quarter of 2020, the company reported positive results from its phase 2 EMPhASIS trial of IMU-838 in relapsing-remitting multiple sclerosis, achieving both primary and key secondary endpoints with high statistical significance. In the first quarter of 2021, Immunic announced that IMU-838 showed evidence of clinical activity in its phase 2 CALVID-1 trial in hospitalized patients with moderate COVID-19. Also, in the first quarter of 2021, the company reported positive top-line data from an investigator-sponsored phase 2 proof-of-concept clinical trial of IMU-838 in primary sclerosing cholangitis which was conducted in collaboration with Mayo Clinic. To date, IMU-838 has been tested in more than 800 individuals and has shown an attractive pharmacokinetic, safety and tolerability profile. IMU-838 is not yet licensed or approved in any country.

**About Immunic, Inc.**

Immunic, Inc. (Nasdaq: IMUX) is a clinical-stage biopharmaceutical company with a pipeline of selective oral immunology therapies aimed at treating chronic inflammatory and autoimmune diseases. The company is developing three small molecule products: its lead development program, IMU-838, a selective immune modulator that inhibits the intracellular metabolism of activated immune cells by blocking the enzyme DHODH and exhibits a host-based antiviral effect, is currently being developed as a treatment option for multiple sclerosis, ulcerative colitis, Crohn's disease, and primary sclerosing cholangitis. IMU-935, a selective inverse agonist of the transcription factor RORγt, is targeted for development in psoriasis and Guillain-Barré syndrome. IMU-856, which targets the restoration of the intestinal barrier function, is targeted for development in diseases involving bowel barrier dysfunction. For further information, please visit: www.imux.com.

**Cautionary Statement Regarding Forward-Looking Statements**

This press release contains "forward-looking statements" that involve substantial risks and uncertainties for purposes of the safe harbor provided by the Private Securities Litigation Reform Act of 1995. All statements, other than statements of historical facts, included in this press release regarding strategy, future operations, future financial position, future revenue, projected expenses, prospects, plans and objectives of management are forward-looking statements. Examples of such statements relating to Immunic's three development programs and the targeted diseases; the potential for IMU-838 to safely and effectively target diseases, including relapsing-remitting or progressive multiple sclerosis; preclinical and clinical data for IMU-838; the timing of current and future clinical trials; the availability, safety or efficacy of potential treatment options for patients with relapsing-remitting or progressive multiple

sclerosis or other conditions, if any; the potential availability and frequency of administration of IMU-838 as a potential treatment for patients with relapsing-remitting or progressive multiple sclerosis or for patients with other conditions; preparations for a clinical phase 3 program for IMU-838 in relapsing-remitting multiple sclerosis; the nature, strategy and focus of the company and further updates with respect thereto; and the development and commercial potential of any product candidates of the company. Immunic may not actually achieve the plans, carry out the intentions or meet the expectations or projections disclosed in the forward-looking statements and you should not place undue reliance on these forward-looking statements. Such statements are based on management's current expectations and involve risks and uncertainties. Actual results and performance could differ materially from those projected in the forward-looking statements as a result of many factors, including, without limitation, the COVID-19 pandemic, risks and uncertainties associated with the ability to project future cash utilization and reserves needed for contingent future liabilities and business operations, the availability of sufficient resources to meet business objectives and operational requirements, the fact that the results of earlier studies and trials may not be predictive of future clinical trial results, the protection and market exclusivity provided by Immunic's intellectual property, risks related to the drug development and the regulatory approval process and the impact of competitive products and technological changes. A further list and descriptions of these risks, uncertainties and other factors can be found in the section captioned "Risk Factors," in the company's Annual Report on Form 10-K for the fiscal year ended December 31, 2020, filed with the SEC on February 26, 2021, and in the company's subsequent filings with the Securities and Exchange Commission. Copies of these filings are available online at www.sec.gov or ir.imux.com/sec-filings. Any forward-looking statement made in this release speaks only as of the date of this release. Immunic disclaims any intent or obligation to update these forward-looking statements to reflect events or circumstances that exist after the date on which they were made. Immunic expressly disclaims all liability in respect to actions taken or not taken based on any or all the contents of this press release.

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