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AC Immune Full-Year 2020 Financial Results Supporting Materials: Development Pipeline Overview

Section 1: Recent pipeline progress

Advancing novel anti-pTau vaccine toward multiple clinical readouts

After demonstrating highly potent interim immunogenicity and safety in 100% of older patients with early Alzheimer's disease (AD), AC Immune is advancing its first-in-class anti-phospho-Tau (pTau) vaccine, ACI-35.030, in a Phase 1b/2a study. Interim findings from the first two dosing groups support further development of ACI-35.030 into Phase 2/3. The Company is currently vaccinating patients in the third and highest dosing group, with further interim results expected by year end.

There will also be an interim readout in Q2 2021 for an alternative pTau vaccine called JACI-35.054, which enrolled AD patients in a separate low-dose cohort. If determined to be additionally beneficial, AC Immune may decide to further develop JACI-35.054.

AC Immune is developing the ACI-35.030 vaccine in collaboration with Janssen Pharmaceuticals, Inc., one of the Janssen Pharmaceutical Companies of Johnson & Johnson**,** under a 2014 licensing agreement to develop and commercialize therapeutic anti-Tau vaccines for the treatment of AD and potentially other Tauopathies.

Anti-Tau antibody semorinemab Phase 2 study in moderate AD patients is ongoing

Genentech, a member of the Roche Group, has completed enrollment in the currently ongoing multicenter, randomized, double-blind, placebo-controlled Phase 2 "Lauriet" study of semorinemab, an anti-Tau antibody, in people with moderate AD. At this time, Genentech continues to work toward the primary completion (last patient, last visit) of the study in 2021.

Anti-Abeta vaccine to advance following Phase 1b study in people with Down syndrome

AC Immune is advancing its novel anti-Abeta vaccine program after showing encouraging top line immunogenicity and safety results in a completed Phase 1b study of ACI-24 in people with Down syndrome (DS). DS-related AD is a key health challenge facing those living with DS and top line results presented recently at a global DS symposium co-sponsored by AC Immune showed immunogenicity (generation of anti-Abeta antibodies) and a positive pharmacodynamic response as measured by an increase in plasma Abeta. ACI-24 was also safe and well tolerated by individuals with DS, with no serious adverse events (SAEs) or evidence for central nervous system (CNS) inflammation, meningoencephalitis, or ARIA (amyloid-related imaging abnormalities), including ARIA-E (-edema) and ARIA-H (-hemorrhage).

Importantly, the successful completion of this first-of-its-kind Phase 1b study demonstrates the feasibility of safely testing the Company's Abeta vaccine in individuals with DS. The high motivation in this community and favorable safety profile of ACI-24 resulted in with a very high clinical trial retention rate with no early subject withdrawals at any dose during the treatment period. AC Immune plans to present the full Phase 1b study data at the upcoming Alzheimer's Association International Conference (AAIC).

Due to the high vulnerability of people with DS to severe COVID-19 sequelae, initiation of the next clinical trial will be delayed to ensure the safety of study participants. In the interim, AC Immune is taking advantage of this time to accelerate development of its optimized anti-Abeta vaccine formulation, which demonstrated encouraging safety and superior immunogenicity results in mouse and non-human primate (NHP) studies. The optimized vaccine formulation primes, boosts and maintains a strong antibody response against key pathological Abeta species (including oligomeric and pyroglutamate Abeta). The antibodies elicited by the vaccine in NHPs showed clear target engagement by binding to human Abeta plaques on AD patient-derived brain tissue.

There is broad potential for the optimized Abeta vaccine across Abeta-driven diseases, including DS-related, genetic (ADAD, autosomal dominant AD), and sporadic AD. AC immune is in discussion with the Food and Drug Administration on a potentially accelerated development pathway for the optimized Abeta vaccine and expects to file an Investigational New Drug (IND) application in Q4 2021. The Company then plans to initiate a follow-on clinical trial in DS with the optimized vaccine formulation as soon as possible, depending on Covid-19.

Optimized Abeta vaccine formulation to support future development in AD

In addition to DS, ACI-24 is currently being tested in a Phase 2 clinical trial in patients with mild AD. In this study, there have been no safety concerns nor evidence for CNS inflammation or ARIA related to ACI-24 in any subject. The Phase 2 study is progressing toward an 18-month interim analysis, which is planned for Q2 2021. AC Immune will complete the study with the 24-month analysis on the basis of currently enrolled patients.

In line with the Company's proven business model, AC Immune plans to complete the current Phase 2 study of ACI-24 in mild AD and seek a strategic partner for further development for this indication. The Company expects the optimized vaccine formulation to support ongoing partnering discussions.

Advancing Morphomer™ Tau aggregation inhibitor program in NeuroOrphan indications and Alzheimer's disease

In November, AC Immune announced that the Phase 1 study of the small molecule Morphomer™ Tau aggregation inhibitor, ACI-3024, had been completed. In the study, which was conducted in partnership with Eli Lilly and Company, single and multiple dosing with ACI-3024 resulted in dose-dependent exposure, achieving potentially therapeutic target levels of ACI-3024 in the cerebrospinal fluid (CSF) at the highest administered dose.

Plans to conduct additional clinical trials with ACI-3024 in AD have been suspended. ACI-3024 will be further evaluated for efficacy in models of rare Tauopathies. The Companies have decided to pursue other promising Tau Morphomer candidates with the desired CSF exposure and selectivity for pathological aggregated Tau for potential clinical development in AD.

Near-term clinical readout planned for first-in-class alpha-synuclein-PET diagnostic

Supported by grant funding from the Michael J. Fox Foundation for Parkinson's Research, AC Immune recently commenced a first-in-human study for its next-generation alpha-synuclein positron emission tomography (PET) tracer, ACI-12589, a first-in-class diagnostic imaging agent for Parkinson's disease (PD) and other alpha-synucleinopathies. The Company expects to report data from this study in Q3 2021. In preclinical studies, ACI-12589 demonstrates significantly improved target occupancy and binds to PD patient-derived tissue with improved sensitivity and specificity compared to the prior PET tracer candidate, positioning ACI-12589 as a potentially game-changing tool for reliable diagnosis and monitoring of disease progression in PD. Further preclinical data for ACI-12589 were presented at the AD/PD™ 2021 conference, showing excellent target engagement and signal specificity on additional patient-derived tissues including multiple system atrophy (MSA) and dementia with Lewy bodies (DLB), as well as desirable pharmacokinetic characteristics in non-human primates.

Advancing the first biologically active alpha-synuclein aggregation inhibitors toward *in vivo* proof-of-concept studies

Leveraging its Morphomer™ platform, the Company has identified and characterized the first biologically active small molecule inhibitors targeting intracellular alpha-synuclein aggregates. These initial compounds significantly decrease alpha-synuclein aggregate formation in cellular assays while demonstrating favorable pharmacokinetic properties that support further assessment of efficacy in *in vivo* animal models. The mode of action, interference with alpha-synuclein fibrillation, has been confirmed by independent protein assays enabling innovative hit-to-lead medicinal chemistry optimization, which is currently ongoing. These preclinical results were presented recently at the AD/PD™ 2021 conference, and AC Immune expects to begin evaluating selected candidates in *in vivo* proof-of-concept (PoC) studies in Q3 2021.

Accelerating development of multiple candidates targeting the NLRP3 inflammasome pathway

AC Immune recently announced key advancements in its small molecule and antibody programs targeting the NLRP3 inflammasome. The Company successfully identified, and filed patent applications for, various chemical series of potent small molecule NLRP3 inhibitors with demonstrated biological activity across multiple functional assays. Furthermore, initial animal studies show highly potent target inhibition in a model of peripheral inflammation, providing the first evidence of *in vivo* activity. AC immune is currently evaluating potential lead compounds for further *in vivo* efficacy and CNS delivery. The Company expects to initiate *in vivo* PoC studies for CNS-

optimized lead compounds for development in AD and other key neurodegenerative diseases by year end, as well as evaluate the potential of a second lead molecule in a clinically relevant non-CNS disease model.

In parallel, AC Immune successfully identified antibodies that bind with high affinity and neutralize a key downstream component of the NLRP3 pathway called ASC (apoptosis-associated speck-like protein containing a C-terminal caspase recruitment domain), which acts extracellularly to exacerbate damage caused by proteinopathies, in particular Abeta. The Company's antibody candidates potently inhibit ASC-mediated inflammatory responses *in vitro*, and selected antibodies will be further evaluated in *in vivo* PoC studies using animal models of human disease, which AC Immune expects to start by year end.

First-in-class TPD-43 therapeutic and diagnostic candidates expected to reach key value-inflection points

AC Immune's novel anti-TDP-43 therapeutic antibody candidates and diagnostic TDP-43 PET tracer candidates are among the most advanced in development with the potential to have a substantial impact on public health. In addition to being a major co-pathology in AD, pathological TDP-43 is also a primary disease driver for NeuroOrphan indications such as amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration with TDP-43 pathology (FTLD-TDP), as well as the very large, recently described indication limbic-predominant age-related TDP-43 encephalopathy (LATE), which causes AD-like dementia in older patients. There are currently no targeted therapies or diagnostics available to address TDP-43 proteinopathies.

The Company's lead TDP-43 antibody candidate is currently in IND-enabling studies, having shown the ability to mitigate TDP-43 neuropathology in a mouse model of TDP-43 proteinopathies. These studies are continuing in 2021 and AC Immune expects to start preclinical toxicology studies by year end. AC Immune is also leveraging its anti-TDP-43 antibodies to develop novel, highly sensitive immuno-assays for the detection and quantification of TDP-43 isoforms in biofluids (blood and/or CSF), which is supported by a highly competitive grant from Target ALS. AC Immune expects to develop the first of these novel immuno-assays by year end.

Further characterization and lead optimization has progressed for AC Immune's first-in-class Morphomer™-derived TDP-43 PET imaging tracers, which demonstrate high affinity binding to brain-derived pathological TDP-43 aggregates as well as direct target engagement within patient brain tissue samples. AC Immune expects to initiate IND-enabling studies for its lead TDP-43 PET tracer candidate in Q3 2021. This program is supported by a highly competitive grant from the 'EU Joint Programme – Neurodegenerative Disease Research' (JPND), and will be conducted in collaboration with the JPND ImageTDP-43 consortium.

Further preclinical results for both the anti-TDP-43 antibody and TDP-43-PET tracer programs were reported during oral presentations at the AD/PD™ 2021 conference.

Section 2: 2021 execution strategy and anticipated milestones

AC Immune's execution strategy is focused on three key initiatives, which support the Company's overarching goal of enabling precision medicine for neurodegenerative diseases:

- The Company plans to accelerate the development of its late-stage therapies in AD in collaboration with its strategic partners, including its novel pTau vaccine with Janssen Pharmaceuticals Inc., which continues to show great promise
- AC Immune is sharpening its strategic focus on non-AD indications with high unmet need. Currently this includes its anti-Abeta vaccine in people with DS, as well as its therapeutic and diagnostic candidates targeting TDP-43 and alpha-synuclein, where the Company may focus in-house efforts on select NeuroOrphan indications while seeking potential partnerships for larger indications like LATE and PD. Furthermore, AC Immune's NLRP3 inflammasome-targeted programs have broad applicability both within CNS and non-CNS indications
- The Company plans to accelerate advancement of its diagnostic candidates to late-stage development, as continued leadership in precision medicine is a key differentiator for AC Immune. These candidates include its Tau, alpha-synuclein, and TDP-43 PET tracers, which potentially enable earlier disease diagnosis, improved clinical trial outcomes and additional revenue generation for the Company

AC Immune's milestones for 2021 are summarized below:

Timing	Program	Target / modality	Indication	Anticipated Milestone
Q1 Achieved	ACI-35.030	pTau vaccine	AD	Phase 1b/2a mid-dose interim analysis
	ACI-24 in AD	Abeta vaccine	AD	Phase 2 interim analysis (12 month)
	ACI-24 in DS	Abeta vaccine	DS-related AD	Top line Phase 1b study results
	a-syn-PET	a-syn PET diagnostic	PD, a-synucleinopathies	Start FiH study
Q2	Semorinemab	Tau antibody	AD	Phase 2 primary completion
	ACI-24 in AD	Abeta vaccine	AD	Phase 2 interim analysis (18 month)
	JACI-35.054	pTau vaccine	AD	Phase 1b/2a low-dose interim analysis
	ACI-3024	Tau small molecule	NeuroOrphan	Select NeuroOrphan indication
Q3	a-syn-PET	a-syn PET diagnostic	PD, a-synucleinopathies	FiH study readout
	Mor-a-syn	a-syn small molecule	PD, a-synucleinopathies	Start *in vivo* PoC studies
	TDP-43-PET	TDP-43 PET diagnostic	NeuroOrphan, LATE	Initiate IND-enabling studies
Q4	ACI-35.030	pTau vaccine	AD	Phase 1b/2a high-dose interim analysis
	ACI-24 in DS	Abeta vaccine	AD	Submit IND for optimized formulation
	Mor-NLRP3	NLRP3 small molecule	non-CNS (undisclosed)	Report *in vivo* PoC in disease-relevant model
	Mor-NLRP3	NLRP3 small molecule	CNS (undisclosed)	Start *in vivo* PoC
	NLRP3-mAb	NLRP3 antibody	CNS (undisclosed)	Start *in vivo* PoC
	TDP43-mAb	TDP-43 antibody	NeuroOrphan, LATE	Initiate IND-enabling toxicology
	TDP-43-biofluid	TDP-43 biofluid diagnostic	NeuroOrphan, LATE	Establish validation ready assay