

Immunic Therapeutics Developing Selective Oral Therapies in Immunology

NASDAQ: IMUX | January 2023

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This presentation contains "forward-looking statements" that involve substantial risks and uncertainties for purposes of the safe harbor within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. These include statements regarding management's intentions, plans, beliefs, expectations or forecasts for the future, and, therefore, you are cautioned not to place undue reliance on them. No forward-looking statement can be guaranteed, and actual results may differ materially from those projected. Immunic undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise, except to the extent required by law. We use words such as "anticipates," "believes," "plans," "expects," "future," "intends," "may," "will," "should," "could," "estimates," "predicts," "potential," "continue," "guidance," and similar expressions to identify these forward-looking statements that are intended to be covered by the safe-harbor provisions of the Private Securities Litigation Reform Act of 1995.

Such forward-looking statements are based on our expectations and involve risks and uncertainties; consequently, actual results may differ materially from those expressed or implied in the statements due to a number of factors, including, but not limited to, risks relating to strategy, future operations, future financial position, future revenue, projected expenses, prospects, plans and objectives of management. Risks and uncertainties that may cause actual results to differ materially from those expressed or implied in any forward-looking statement include, but are not limited to: Immunic's plans to develop and commercialize its product candidates, including IMU-838, IMU-935 and IMU-856; the timing of initiation of Immunic's planned clinical trials; the potential for IMU-838 and the Company's other product candidates to safely and effectively target and treat the diseases mentioned herein; the impact of future preclinical and clinical data on IMU-838 and the Company's other product candidates; the availability or efficacy of Immunic's potential treatment options that may be supported by trial data discussed herein; expectations regarding potential market size; the timing of the availability of data from Immunic's clinical trials; the timing of any planned investigational new drug application or new drug application; Immunic's plans to research, develop and commercialize its current and future product candidates; Immunic's ability to successfully collaborate with existing collaborators or enter into new collaboration agreements, and to fulfill its obligations under any such collaboration agreements; the clinical utility, potential benefits and market acceptance of Immunic's competitors and industry; the impact of government laws and regulations; COVID-19 and the armed conflict in Ukraine; Immunic's ability to protect its intellectual property position; Immunic's estimates regarding future revenue, expenses, capital requirements and need for additional financing; the nature, strategy and focus of the company; an



Forward-looking statements included in this presentation are based on information available to Immunic as of the date of this presentation. Immunic does not undertake any obligation to update such forward-looking statements except as required by applicable law.



Our Mission



We are developing a pipeline of nextgeneration selective oral therapies focused on offering patients with chronic inflammatory and autoimmune diseases new and clinically meaningful treatment options.





Leadership Team



Company is Led by an Experienced Management Team

Duane

Nash, MD,

JD, MBA

Executive

Chairman



Vitt, PhD CEO & President





Muehler, MD, MBA СМО

Patrick

Walsh

CBO

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Joerg Neermann, PhD Independent Director







Daniel Vitt, PhD CEO & President of

Immunic







Tamar Howson, CFA Independent Director

Maria Törnsén Director





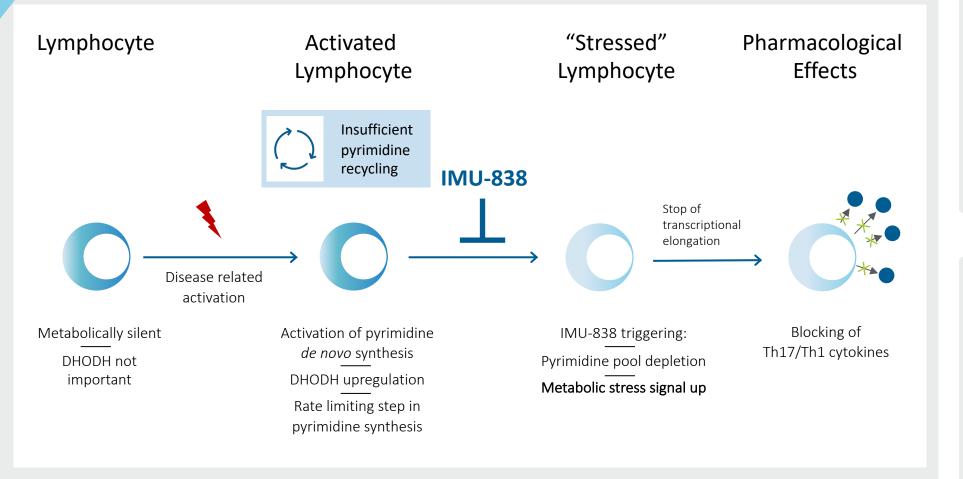
Advanced Clinical Pipeline

Three Differentiated Programs in Various Phases of Clinical Development

Program	Target	Preclinical	Phase 1	Phase 2	Phase 3	Key Milestones
		Relapsing Multiple Scler	rosis (RMS) – ENSURE T	 Initial phase 1b celiac disease data of IMU-856 expected in 2023 		
Vidofludimus Calcium (IMU-838)	DHODH	Progressive Multiple Sc	erosis (PMS) – CALLIPE	R Trial	I	 Interim analysis of CALLIPER trial in PMS planned after half of the patients completed 24 weeks of treatment,
	IL-17 / RORγt					estimated for H2/2023
IMU-935		Psoriasis				 Interim analysis of first ENSURE trial in RMS planned after approximately half of the events occurred
		Castration-Resistant Pro	ostate Cancer (CRPC)			 CALLIPER trial estimated to readout end of 2024
IMU-856	Intestinal Barrier Function	Celiac Disease				 ENSURE-1 trial estimated to readout end of 2025, ENSURE-2 soon thereafter



Vidofludimus Calcium Selectively Targets Only Hyperactive Immune Cells



Preserves normal
 immune cell function
 and numbers
 → No nonspecific
 immunosuppression
 → Maintains
 vaccination
 efficacy^[1]
 → No negative effect

No negative effect observed on white blood cell count or rates of infection or malignancies

Illustration adapted from Tan et al., 2016, Mol Cell 62; [1] Bar-Or A, Freedman MS, Kremenchutzky M, et al. Neurology. 2013;81(6):552-558 DHODH: dihydroorotate dehydrogenase; Th: T helper



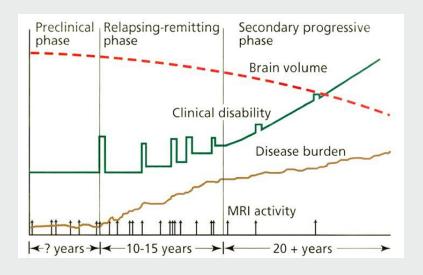
Vidofludimus Calcium in Multiple Sclerosis (MS)

Targeted to Elevate the Standard of Care With a Holistic Solution for the Full Spectrum of MS Patients

For Patients With Lifelong Illness, Disability is a Critical Concern

MS is a Lifelong Disease and Starts Early

- Lifelong disease requiring decades of therapy
- ~2.8 million people affected worldwide (~1M in US)^[1]
- Often diagnosed in younger adults (3:1 women:men)





Therapeutic Goal: Preventing Disability Worsening

- Unmet need is prevention of disability worsening
- Historical focus has been on prevention of relapses via broad immunosuppression



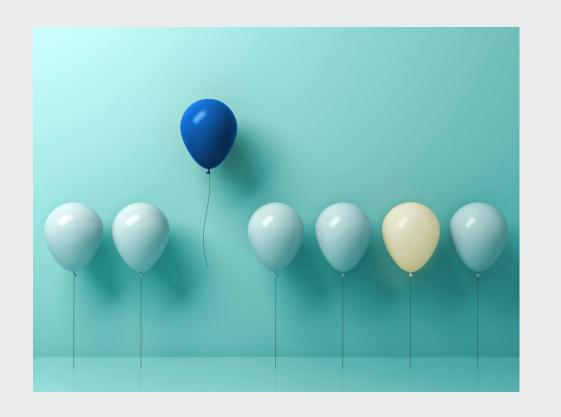
- Problematic side effects
- Cumulative health risks: cancer, infections, cardiovascular and liver disease
- Need for significant monitoring

[1] MS International Federation (2020): Atlas of MS. https://www.atlasofms.org/map/global/epidemiology/number-of-people-with-ms; illustration adapted from Fox RJ, Cohen JA. Cleve Clin J of Med, 2001; 68:157–70 PML: progressive multifocal leukoencephalopathy; M: million



Vidofludimus Calcium Aimed to Go Above and Beyond Current Care to Comprehensively Address Patients' Needs

Targeted to Elevate the Standard of Care With a Holistic Solution for MS Patients



Uniquely matched to the multi-faceted neurodegeneration of smoldering and active MS

- Anti-viral effects
- Anti-inflammatory effects
- Neuroprotective effects

Seeks to provide unrivaled safety, tolerability & convenience

 Targeted to set the new standard for patient preference, exceeding all options including glatiramer acetate



Vidofludimus Calcium Addresses Multiple Drivers of Neurodegeneration in MS Patients

1 Anti-Inflammatory Effects

- Selectively targets
 hyperactive immune cells
- Reduces MRI lesions
- Reduces relapses
- Mechanism already shown to reduce brain atrophy

Vidofludimus calcium can target various aspects of 'smoldering' MS

3 Direct Neuroprotective Effects

New data showing impact on validated neuroprotective target
 Impact on serum neurofilament
 Encouraging clinical signals from phase 2 trial on change in EDSS

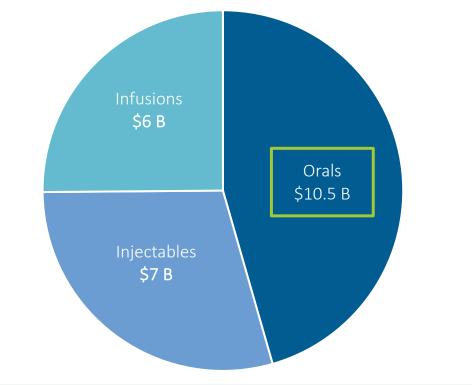
Anti-Viral Effects

- Broad-spectrum antiviral activity established
- EBV linked to MS
- Vidofludimus calcium with potent anti-EBV activity



The Global MS Market Exceeds \$23B in Annual Sales, With \$1B+ Contributions from Multiple Brands

Oral Drugs Represent Most Significant Share of Total Sales in Major Territories (2020)



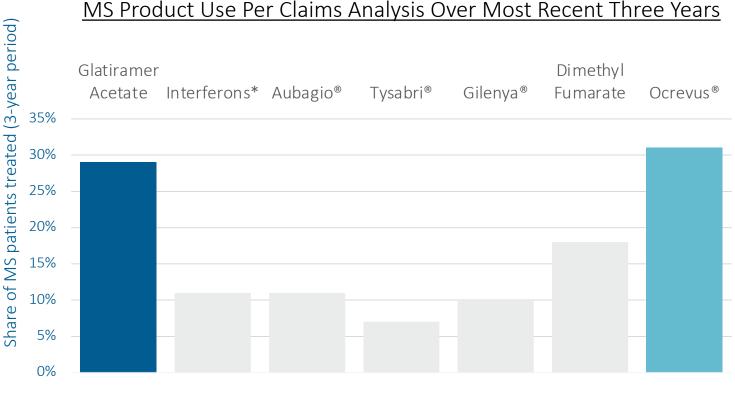
* Sales numbers in G7 countries (US, UK, Canada, Japan, Germany, France, Italy) in USD billion; S1P: sphingosine-1-phosphate Source: Multiple Sclerosis Landscape and Forecast by Decision Resources Group Part of Clarivate Most brands are generating in excess of \$1 billion in global annual sales in 2021, with most sales coming from the U.S.

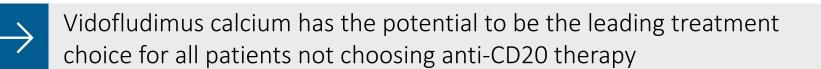
- Ocrevus[®] \$6.3 billion
- Tecfidera[®] & Vumerity[®] \$2.4 billion
- Tysabri[®] \$2.1 billion
- Gilenya[®] \$2.8 billion
- Aubagio[®] \$2.0 billion
- Avonex[®] & Plegridy[®] \$1.6 billion
- Rebif[®] \$1 billion



The Majority of Patients Have Exposure to Either Glatiramer Acetate or Ocrevus®

- Relapse prevention is NOT the only unmet need
 - Despite lack of effect on relapses, glatiramer acetate is the second most commonly used disease modifying therapy
- Ocrevus[®] leads the market with a significant impact on relapses and a label in primary progressive MS patients
- Other therapies come with significant tradeoffs in effect size, or more notably, the safety and tolerability profile



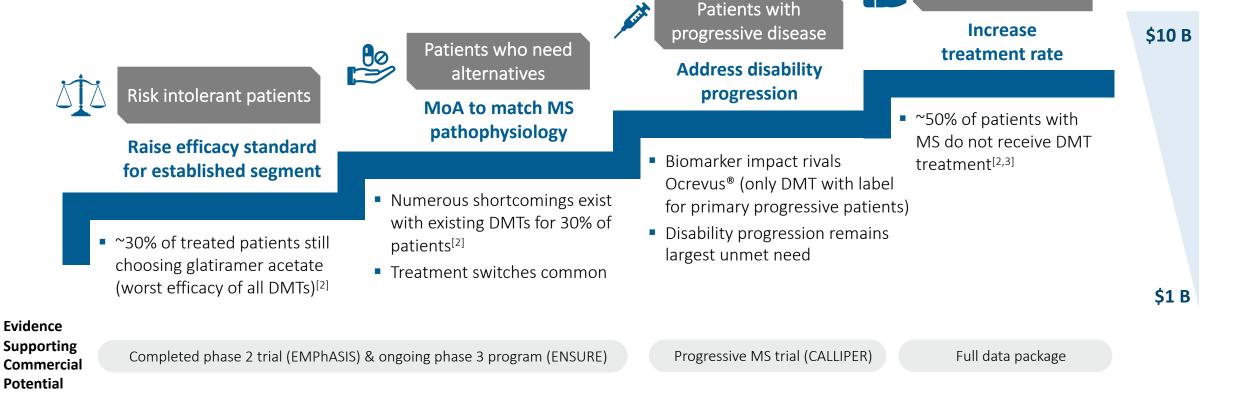


Source: Patient treatment exposure data based on proprietary research performed in partnership with Trinity Partners & utilizing Komodo Health claims data analysis, 2022. All % of patients without relapses provided per product labels. Dimethyl fumarate result is an average of the rates from two Phase 3 studies. *Interferons share of patients treated includes combined Avonex® and Rebif®-treated patients. % of patients without relapse at 2 years based on rate for Avonex®. CD20: B-lymphocyte antigen



The Unmet Needs in MS Encompasses Multiple Patient Segments

725,000 US diagnosed MS patients^[1] Multiple opportunities to address unmet needs of patients



[1] Company estimates leveraging Briggs, F. B., & Hill, E. (2019). Multiple Sclerosis Journal & Wallin, M. T., Culpepper, W. J., Campbell, J. D., Nelson, L. M., Langer-Gould, A., Marrie, R. A., & Buka, S. L. (2019). Neurology, 92(10), e1029-e1040.
 [2] Proprietary research performed in 2022 in partnership with Trinity Partners and utilizing Komodo Health claims data analysis [3] Fox RJ, Cosenza C, Cripps L, Ford P, Mercer M, Natarajan S, Salter A, Tyry T, Cofield SS. Neurology. 2019 Apr 2;92(14):e1634-e1642 DMT: disease modifying therapy; MoA: mode of action; B: billion



Market

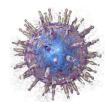
Opportunity

Untreated patients

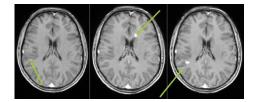
Substantial Progress in Understanding Multiple Sclerosis Four Key Publications in 2022 Impacting Our Knowledge – and Options to Treat

EBV Infection is a prerequisite of MS^[1]

Development of **crossreactive antibodies** against EBNA1 and GlialCAM^[2] PIRA (Progression Independent of Relapse Activity): Major portion of disability worsening is independent of relapses^[3]







[1] Bjornevik K. et al., Science. 10.1126/science.abj8222 (2022) [2] Lanz, T.V., et al. Nature 603, 321–327 (2022) [3] Fred D Lublin et al., Brain, 2022;, awac016 EBV: Epstein-Barr Virus



Key Publications in 2022 Provide Clear Evidence of a Direct Link Between Epstein-Barr Virus and MS



Epstein-Barr Virus (EBV) is Essential for Onset of MS and Involved in Ongoing Autoimmunity^[1,2]

- Epidemiologic study showed a clear association between EBV infection and occurrence of MS^[2]
- 32-fold increased risk in EBV-infected patients^[2]
- Cross-reactive antibodies between EBV antigen EBNA1 and CNS protein GlialCAM found in the CSF of MS patients^[3,4]
- EBV infection and reactivation seems to be an ongoing trigger for the immune system in MS patients^[5]
- MS is not only preceded by EBV infection, but also associated with broader EBV-specific T cell receptor repertoires

Science	REP	M75	Article				
Cite as: K. Bjomevik et al., Svinov 10.1126/science.abj1222 (2022).					lls in multiple A1 and GlialCAM		
Longitudinal analysis revea	ils high prevalence of						
Epstein-Barr virus associat	ed with multiple sclerosis		https://doi.org/10.1038/s41586-022-0443	1.7 Tobles V Local M. B. Co.	nille Brever'', Peggy P. No', Jae Georg Moon'', Kevin M. Jude',		
Stephen J. Elledge ⁴ , David W. Niebuhr ^a , Ann I. Sch			Received: 6 August 2021 Accepted: 14 January 2022	Daniel Fernandez", Ricar Christopher M. Bartley", Manael tyer", J. Brodley : Loran B. Kley", Victoria	do A. Fernandos", Alejandro M. Gernas'", Gabriel-Stofan Naeji", Ryan D. Schubert', Isobel A. Haves', Sers E. Vacquez'', Euchero'', Blanca Teogen'', Jeffrey E. Dunr'', Christopher B. Lock'', C. Carbard', Blanca M. Michenbalde', Blaka T. Arbah''.		
Department of Nutrition, Harvant T. H. Chen School of Public Health, Booton J. USA: Department of Neurology, Harvard Medical School, Boston, MA, USA 19 Policinic, MS Center and Pessach Center for Dinical Neuroimmunology and S- Neuroscient, Chosen of Centerics, Scholane and Women Linearch Heavert His	di, USA. "Partners Multiple Sciences Center: Program and Biomeric Hospital Footm Million existintics: Center: Macachusetts General Hospital Bodon, MA, USA. "Reunslop: China Innovations David (CC201): University Hospital Bodo, University of Basic Book gline Macali Institute. Geopartners of Genetics, and "Hospital" Institute. Texes of Experimental Development of Hospital Paral. University of Basic Hospital Institute. Geopartners of Genetics, and "Hospital Neurosci, Nancal Hospital Hospital Institute. Comparison of Hospital Development and Hospital Development. Nancal Hospital Institute.	nd	Published online: 24 January 2022	Mark 1. Anderson", Jose	ph L. Defini ^{nter} , Michael R. Wilson [*] , Rachael J. M. Bashford Rogars [®] , Bristopher Garcia [*] , Lawrence Steinenan [®] & William H. Bobinson ^{1/411}		
H. Chan School of Hubic Health, Bolson, MA, USA, "Department of Vathology, Privatehae Medicine and Biolatantics, Uniformed Services University of the He of Public Health, Boston, MA, USA, "Channing Lidenatory, Department of Medi (Channing), Department of Medicine).	Intert of Epidemiology, and Department of Intrunology and Infectious Diseases. Harvard Brytherizer Wome's Hospital, Harvard Medical School, Bostons, MU, USA, Wegartment of Mit Sciences, Berlenda, MU, USA, "Department" of Epidemiology, Harvard T. H. Chan Sch one, Brytham and Wamer's Hospital, and Harvard Medical School, Boston, MA, USA.	7. 22		autoreactive lymphoc B lymphocytes in the	i) is a heterogenous autoinnmune disease in which ytes attack the myelin sheath of the central nervous system, cerebrospinal fluid (CSF) of patients with MS contribute to		
These authors contributed equally to this work. These authors contributed equally to this work.		ov ala		infection has been epi	rete oligoclonal immunoglobulins ¹³ . Epstein–Barr virus (EBV) demiologically linked to MS, but its pathological role		
*Corresponding author. Erwait asscherillihigh harvard edu		and for		remains unclear ³ . Her	e we demonstrate high affinity molecular minicry between factor EBV nuclear antigen 1 (EBNAL) and the central nervous		
unknown etiology. We tested the hypothesis that comprising more than 10 million young adults on diagnosed with MS during their period of service. was not increased after infection with other virus	Risk of MS increased 32-fold after infection with EBV bu es, including the similarly transmitted cytomegalovirus.	e legedwww.ad		system protein glial co in vivo functional evid was initially identified repertoire of MS bloo	ell adhesion molecule (GluilCAM) and provide structural and lence for its relevance. A crois-reactive CSI-derived antibody by single-cell sequencing of the paired chain B cell and CSI, followed by protein microarray-based testing of sed CSI-derived antibodies against MS-associated viruses.		
EBV seroconversion. These findings cannot be ex	arker of neuroaxonal degeneration, increased only after	SNICL		Sequence analysis, aff	inity measurements and the crystal structure of the EBNAI-		_
as the leading cause of MS.	Science			peptide epitope in the development o			
Multiple sclerosis (MS) is a chronic inflammatory de	Contact			GlialCAM cross-rea post-translational		¢ JEM ==−	
linating disease of the central nervous system of unka etiology. The demyelination in the brain and spinal cord		Cite a Science 1		disease in a mouse prevalent in patien	BRIEF DEFINITIVE REPORT	Jy JERTING	
immune-mediated process (I) possibly triggered by a vir fection (2). Among the putative causal agents, the top e				association betwee therapies.	Broader Epstein-Barr viru	e enerifie T cell recentor	
date is Epstein-Barr virus (EBV) (3). EBV is a bi herpesvirus that after infection persists in latent form	Epstein-Barr virus and multip	le sclerosis		therapies.			
lymphocytes throughout the life of the host (3). A causa of EW is summerted by the increased MS risk after infer	William H. Robinson ^{1,2} and Lawrence Steinman ²		The oversence of elipsclonal bands (OC	talia CSE and the efficience	repertoire in patients wit	n multiple sclerosis	
mononucleosis (4), elevated serum antibody titers ag	Ovision of Innunskipg and Rheumatology, Department of Medicine, Stanford Universit "Department of Neurology and Neurological Sciences, Stanford University, Stanford, CA	y, Stanford, CA, USA, NA Palo Altu Health C USA. Enroll is cohorceally factored why she	of therapies that deplete B cells emp B cells in the pathobiology of MS ¹ . An	hasize the importance of	Töman Schneider Hohendorf? O, Lika Ann Gerden ^{13,44} O, Biatrice Pigeo	árt ¹⁺ ©, Rahul Gitalman ^a ©, Patrick Ozkamp ¹ ©, Flarian Rubelt ¹ ©,	
EBV nuclear antigens (EBNAs) (5), and by the presen EBV in MS demyelinated lesions reported in some (6-8	Infection with Epstein-Barr virus is the trigger for the d		mumps, measles, varicella zoster viru present in MS ¹¹ , but their relevance is un	s (VZV) and EBV are often	Catarina Raposo ⁴ 0, Björn Tackerberg ⁶¹ 0, Marianne Repenhausen ⁶ 0, Andrea Fled-Hische ¹¹⁴ 0, Eduardis Behran ¹¹⁴ 0, Taria Kanafel ¹¹⁴ 0, K	Cisudia peroschia®O, Christian Wansch®O, Horence Bucciarebi®O, Jatja Andinger®O, Cathanna C. Gross®O, Heid Chapman®O, Lan Kaplan®O,	
not all (9), pathological studies. Evidence of causality, ever, remains inconclusive.			titters can be detected in nearly 100% of	f patients with MS before	Cavid Bassat ⁴ 0 , Ratmat Weierle ¹¹⁴ 0 , Mattin Kerschentarioe ¹¹⁴ 0 , La Henry Wend ¹⁴ 0 , and Nicholas Schwab ¹⁴ 0	usa Kotz ¹ 0 , Jan D. Linemann ¹ 0 , Renhard Hobbeld ¹¹ 0 , Roland L&lau ¹⁴ 0 ,	
Causality implies that some individuals who devel	postulated to trigger multiple scierosis (MS) (1). Prior anal-	plasmablasts and plasma cells. The mechanism (or mecha	the development of clinical symptoms, y an epidemiological link between MS ars tious menonucleosis during EBV infect	IEBV". Symptomatic infec-			
MS after EBV infection would not have developed MS if had not been infected with EBV. Ruling out a randor	yses demonstrated increased serum antibodies to EBV in -99.5% of MS patients compared with -94% of healthy indi-	development remains elusive. I mimicry, through which EBV	developing MS'. Molecular mimicry betw	een virus and self-antigens	infection to CNS autoimmunity. As an altered anti-EBV T cell r	s (MS) pathology and cross-reactive antibodies might link EBV reaction was suggested in MS, we queried peripheral blood T cell.	
trial, the gold standard to study this counterfactual o rence is an "experiment of nature." a longitudinal inve-	viduals (2). On page XXX of this issue, Bjornevik et al. (3)	human myelin proteins and of induce autoimmunity against	Antibodies against certain EBNAI re- patients with MS, including the region	tions have been found in	receptor # chain (TCR#) reportoires of 1,395 MS patients, 88 multimer-confirmed, viral antigen-specific TCR# sequences. V	7 controls, and 35 monazygotic, M5-discondant twin pairs for the detected more MMC - contricted ERV specific TCMD	
tion of MS incidence in a cohort of EEV-negative individ	developed MS among a cohort of >10 million people active in	EBV transformation of B cells of	(refs. ¹⁷⁻⁰), which we describe here in or lar mimicry between EBNA1 and Gliak				
some of whom will be infected with EIV during the fo up and some who will not. The ubiquitous nature of	of the 801 MS cases were initially KRV seconegative, and 34	sion of pathogenic plasmablas through disruption of several	cance of this mimicry in the pathophy	AM. The potential signifi- iology of MS is described	discerdant far MS. Anti-VLA-4 treatment amplified this obse modulate EBV-specific T cell occurrence. In healthy individua	rvation, while interferon \$- or anti-CD20 treatment did not is, E8V-specific CD8* T cells were of an effector-memory	
which infects -95% of adults, and the fact that MS is a tively rare disease, has until now impeded sud	became infected with EBV before the onset of MS. EBV sero-	brane protein 2A (LMP2A) min	in detail.		phenotype in peripheral blood and cerebrospinal fluid. In MS	patients, cerebrospinal fluid also contained EBV-specific central-	
and a second	ment, with only one of 801 MS cases being EBV seronegative	naling. LMP1 mimics CD costimulatory pathway that is	A locial afficiency appears at the ord of the paper.		memory CDB' T cells, suggesting recent priming. Therefore, I with broader EBV-specific TCR reportaines, consistent with a	MS is not only preceded by EBV infection, but also associated n ongoing anti-EBV immune reaction in MS.	
First release: 13 January 2022	at the time of MS onset. These findings provide compelling	teraction. Additionally, EBV e protein, which activates B cell					
	MS.	mediate bystander damage to			Introduction		
	disease of the central nervous system (CNS)? In MS, there is	sheath, or defective clearance o specific for EBV lytic proteins a	re present in MS brain lesions.		EBV seroconversion has been shown in large epidemiological studies to preorde clinical signs of multiple sclerosis (MS;	subsequent recruitment of peripheral cytotonic as well as T helper cells (Bar-Or et al., 2020). It has been suggested previously	
		and a persistent EBV infection CD8' T cell responses that med			Bornevik et al., 2022; Levin et al., 2010), confirming that EBV	that peripheral T cells show increased cytokine response to la-	
	jured. In MS, B cells and their activated progeny,	figure).	AND DECK DECKED OF BUILDED		infection is necessary but not sufficient for disease initiation and associated central nervous system (CNS) damage. Additionally,	tent ESNA-1 epitopes (Lunemann et al., 2006) with presumed cross-reactivity to myelin (Lunemann et al., 2008). However, II	
	plasmablasts, express integrin a4, which has adhesive prop- erties that allow these antibody-producing cells to move from	There are multiple report mimicry might induce MS. Se	is suggesting that molecular		antibody cross-reactivity was detected between a latent viral	has also been discussed that the anti-EBV T cell response in MS patients targets lytic components, indicating copping LBV ac-	
	the bone marrow to the peripheral circulation and then	tients to the EBV small capsid p	rum antibonies from MS pa-		autoantigen (GlialCAM) in a subart of patients as a hamoral	tivity (Angeliei et al., 2013; Laurenann et al., 2011) and/or in-	
	across the blood-brain barrier (BBB), where they take resi-	the cytoplasmic protein septin	-9 and are associated with de-		component of and potential link to MS pathology (Alsiei and Salvetti, 2022; Lans et al., 2022). While relaying constiting MS	sufficient EBV control (Cencioni et al., 2007; Pender et al., 2009).	
	feature of MS is the synthesis of immunoglobulins by clonal	myelination (10). Another stu from MS patients are cross-read	tive between amino acids 411-		(ERMS) is specifically characterized by the presence of B- and		
		440 of the viral protein EBV n			plasma cells in the corebrospinal fluid (CSF; Gross et al., 2020), T cells and macrophages dominate CNS immune cell infibrates in	Quantification of EBV specific, MHC-I-restricted TCRB sequences	
	tients with MS, are applied to an electrophoretic gel, they	the human chloride-channel p which is associated with electr	rical conduction in axons (11).		MS (Kuhhmann et al., 2008) and relayses are associated with	in HLA A*02-positive MS patients and healthy centrols In links of the finding that EW infection precedes the develop-	
	form bands of restricted mobility, called oligocional immuno-	MS serum antibodies targeting cross-react with meelin basic r	EBNA-1 residues 411-426 that			is light of the finding that EPV intection precedes the develop- ment of MS and that some MS patients showed cross-reactive	
	mablasts. These antibodies target myelin-producing glial	cross-react with myelin basic p fied (12). Clonally expanded an					
	cells, thereby damaging them (4).	tients targeting EBNA-1 resid	ues 386-405 that cross-react		Tepartment of Neurology with Institute of Translational Neurology, University of W and Bioriedical Center, scalarge Maximilians Universitiet Manchen, Marich, Genters	Series, Weiter, Germany, "Unitation of Chock Microsoftwared by South Sciences, Series and Sciences, Sciences, Telescond, Marchen, Commun. Tradination treatment for the series of the se	
		with the CNS cell adhesion n been described (4). It is intrigu			Martmond, Germany: "Manich Claster of System Neurology Dylengs, Manich, University of Toulouus, Genere National de la Recherche Sciencifique, Indoist Nation	Germany: "Trailouse tretticie for orfectious and inflammatory diseases (Infinity), al de la Sense et de la Recherche Médicale, Université Paul Saltatier, Trailouse, France,	
	of B cells with EBV initiates the pathology seen in MS is now	gions of mimicry have been reg	ported in a small region of the		"Heaptive Extendingers, Seattle, WA, "Roche Sequencing Solution, Pleasanton, of Neurology, Marburg, Germany, "Prostitute of Legal Mathems, Ludwig Masimila	CA, "P. Permann va Riche LM, Besti, Switzerland, "Philippi Generate, Department an Universität Marchen, Marich, Germany, "Institute for Biological Intelligence,"	
	ripe for a deeper understanding of the roles of these clonally expanded B cells and plasmablasts. Depletion of B cells with	EBNA-1 protein; this may arise in a process called epitope spre	through immune surveillance				
	monoclonal antibodies targeting CD20 has emerged as one of	Increased incidence of EBT	V infection is associated with		*1. Schnide Hshendorf, L.A. Gerdin, B. Pignolet, R. Ublas, H. Werell, and N. Schnides an head-plakement to dis.	head contributed equally to this paper. Convequendence to Nicholas Schwab.	
	the most efficacious therapies for MS (7). However, because of the BB8, CD20 monoclonal antibody therapies do not	other autoimmune diseases, in matosus (SLE). Serologic react	cluding systemic lupus erythe-		© 2022 Schweider-Hahendorf et al. This untille is available under a Deather Commer Jerenaus Review 202	in Conver Data Button 4.3 International, as described at https://tynatioecommune.org/	
	reach the CNS in sufficient amounts, and moreover, antibod-	EBV serum antibodies after re					
	ies to CD20 do not deplete their progeny, antibody-producing				Recharduller University Press J. Dep. Med. 2022 Vol. 229 No. 11 e30220650	to anima https://doi.org/20.3284/jew.20220450	Loft
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[1] Lublin FD, et al. Brain. 2022 Sep 14;145(9):3147-3161 [2] Bjornevik K. et al., Science. 10.1126/science.abj8222 (2022) [3] Lanz, T.V., et al. Nature 603, 321–327 (2022) [4] Robinson WH, Steinman L. Science. 2022 Jan 21;375(6578):264-265 [5] Schneider-Hohendorf et al. J. Exp. Med. 2022 Vol. 219 No. 11 e20220650; EBV: Epstein-Barr Virus; CNS: central nervous system; CSF: cerebrospinal fluid



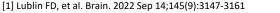
Most Disease Progression is Independent of Relapse, Even in Early RMS Another Key Publication in 2022



New Understanding of Drivers of Long-Term Patient Outcomes^[1]

- Longstanding belief that the disability worsening process is only driven by relapse activity in RMS Patients
- New analysis of 35,000+ patients identifies MS as "smoldering disease"
 - Occurs in absence of relapse activity in RMS patients
 - Contributes to half of disability accumulation in RMS
 - Dominant driver of disease worsening in SPMS, PPMS
- Elevates the importance of any drug that:
 - Reduces relapse activity AND influences the relapse-independent accumulation of neurological deficits (measured as disability worsening and brain atrophy)

https://doi.org/10.1093/brain/awac016	BRAIN 2022: 00; 1-15 1
BRAIN ORIGINAL ARTICLE	Ŕ
How patients with multiples disability Pred D. Lublin, ^{1,1} Dieter A. Häring, ^{2,7} Habib Gang Parhad Hatami, ³ Dieter A. Häring, ^{2,7} Piet Aarden, ² Douglas L. Arnold, ⁶ Heinz Wiendl, ⁶ Tanuja Chim Bernd C. Kieseier ² and @Robert A. Bermel ²	ahi, ³ @Alex Ocampo, ² Frank Dahlke. ²
These authors contributed equally to this work.	
Patients with multiple sclerosis acquire disability either through relapse - independent of relapse activity (PIRA). This study addresses the relative cc independent of relapse activity (PIRA). This study addresses the relative cc delay disability accumulation. Using the Novarias Oxford multiple sclerosis (RO MG) data pool spanned Using the Novarias Oxford multiple sclerosis (RO MG) spanned Toisis 27000 patients with Si Yeara follow-up. We analyzed three disatest (i) vational and monitorized corrolled clinical trials in which disability and phase 3 clinical trials (n= SMG); and (ii) all placebo- controlled phase 5 c relative importance of AAW and PRA, investigated the relative sing Andersen-cill models and observed the impact of the mechanism of w on the time to resch milestone disatibility levels using time continuous M PIRA stated early in the disease process, occurred in all phenotypes an accumulation in the progressive phase of the disease. Relapses signific- ability worsening events, following a year in which relapses occurred (v increased by 11-484 (all # -0.001). Proceeding disease statest ability and data cap were the schedule of the disease statest and the disease process, for placebo-treated patients with milinar disa creased furtistation in walking ability (EDS 54) and 14.48 years to reque patible. All dis 0.50 years (All 40 events to the science statest ability work of the conversion of the All events to the science statest ability work with Dirak events; the fastest transitions were observe relapses. Our data confirm that relapses contribute to the accumulation of disab PIRA begins in relapsing-remitting multiple sclerosis and becomes the of as the disease evolves. Fre-existing disability and older age are the prin cumulation. The use of disease more disolity in the Disputibility sclerosis.	ntribution of relapses to disability worsen- tantic to which multiple sclerosis therapies ing all multiple sclerosis phenotypes and Hty Status Scale (EDSS) transitions from A full analysis dataset containing all obser- ries of the states of the states of the states of the son all cause disability worsening using orening and disease-modifying therapies arizer models. d became the principal driver of disability multiple sclear of all-cause dis- strot models. d became the principal driver of disability multiple sclear of all-cause dis- tribution of the state of all-cause dis- tribution of the state of all-cause dis- tribution of the sclear of all-cause dis- tribution of the state of all-cause dis- tribution of the state of all-cause dis- tribution of the sclear of all-cause dis- tribution of the state of all-cause dis- tribution of the state of all-cause dis- tribution of the sclear of all-cause dis- tribution of the state of all-cause dis- tribution of the state of all-cause dis- tribution of the sclear of all sclear of all sclear of all sclear of all sclear of all sclear of all sclear of all sclear of all sclear distribution of the sclear of all sclear of all sclear of all sclear of all sclear of all sclear distribution of all sclear of all sclear of all sclear distribution of all sclear of all sclear of all sclear distribution of all sclear of all sclear of all sclear of all the functions of the sclear of all sclear of a
1 The Corinne Goldsmith Dickinson Center for Multiple Sclerosis, Ic New York, NY, USA	ahn School of Medicine at Mount Sinai,
Received September 24, 2021. Revised December 01, 2021. Accepted December 16, 2021. Advant & The Antony 2022. Multised by Oxfard University Press on behalf of the Guarantees of Brain. This is an Open Accessive article distribution used in the stress of the Accessive Common Accessive by solv 64, junctional accession of the Accessive Common Ac	Commercial License (https://creativecommons.org/licenses/



RMS: relapsing multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis

Straightforward Approval Strategy in Multiple Sclerosis Enables Clear Demonstration of Effect on Smoldering MS

Phase 3 ENSURE Program in RMS^[1]

- Two identical pivotal trials in RMS patients
- Goal: Low risk clinical program for regulatory approval of vidofludimus calcium
- Dosage: 30 mg vidofludimus calcium QD

Phase 2 CALLIPER Trial in PMS^[2]

- Phase 2 trial in PMS patients
- Goal: Demonstrate vidofludimus calcium's potential for neuroprotective activity in a non-relapse setting
- Dosage: 45 mg vidofludimus calcium QD

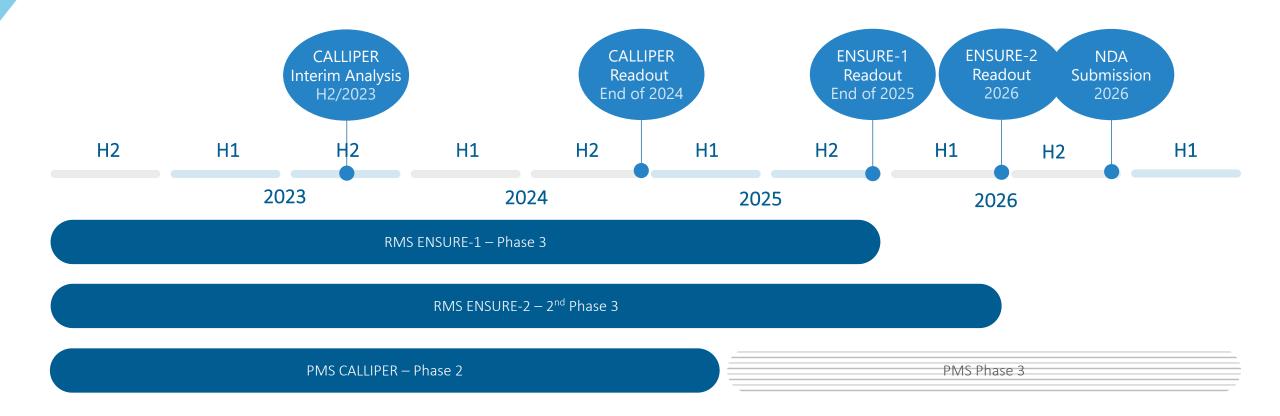
Intended to Provide a Straightforward Path Towards Potential Regulatory Approval:

- Immunic believes that the phase 3 ENSURE program provides a straightforward path towards regulatory approval of vidofludimus calcium in RMS.
- CALLIPER is designed to corroborate vidofludimus calcium's neuroprotective potential to support the drug's unique profile.

[1] ClinicalTrials.gov: NCT05134441 & NCT05201638;
 [2] ClinicalTrials.gov: NCT05054140
 RMS: relapsing multiple sclerosis; PMS: progressive multiple sclerosis; QD: quaque die = once-daily



Straightforward Path Towards Potential Approval



These timelines are current estimates and depend on numerous factors which are not always under our direct control.



ENSURE Program: Ongoing Pivotal Phase 3 Trials in RMS NCT05134441 & NCT05201638



Coordinating Investigator

Robert J. Fox, M.D. **Cleveland Clinic**



Included Patient Population: Relapsing Forms of MS

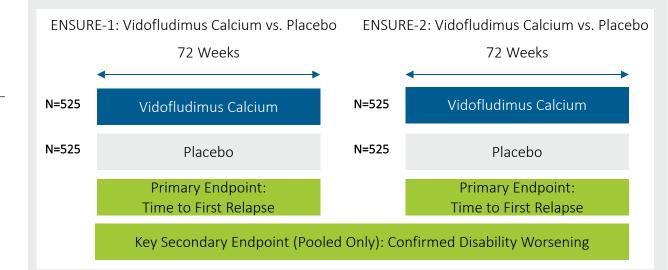
- Adult patients aged 18 to 55 years
- Established diagnosis of MS (Revised McDonald criteria 2017)
- Confirmed relapsing MS (1996 Lublin criteria)
- Active disease as defined by Lublin 2014
- EDSS score at screening between 0 to 5.5

Lublin FD, et al. Neurology. 2014;83(3):278-286 EDSS: Expanded Disability Status Scale; QD: guague die = once-daily



Two Multicenter, Randomized, **Double-Blind Phase 3 Trials**

- Approximately 1,050 patients in each trial
- More than 100 sites in the United States, Latin America, Central and Eastern Europe, and India in each trial
- Randomization to 30 mg vidofludimus calcium or placebo QD





CALLIPER Trial: Ongoing Phase 2 Trial Intended to Complement the Phase 3 Program in RMS



Coordinating Investigator

Robert J. Fox, M.D. Cleveland Clinic



Included Patient Population: Progressive Forms of MS

- Adult patients aged 18 to 65 years
- PPMS or SPMS diagnosis (Revised McDonald criteria 2017)
- EDSS score at screening between 3.0 to 6.5
- No evidence of relapse in last 24 months before randomization
- Evidence of disability progression

Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial*

- Approximately 450 patients in more than 70 sites in North America, Western, Central and Eastern Europe
- Randomization to 45 mg vidofludimus calcium or placebo QD
- Primary endpoint: annualized rate of percent brain volume change up to 120 weeks

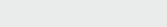


Treatment Schedule

- Blinded 120-week main treatment period
- Optional, approximately 8-year, open-label extension period
- Interim analysis of serum neurofilament light chain planned after approximately half of the enrolled patients have completed 24-weeks of treatment

* NCT05054140

PPMS: primary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis; EDSS: Expanded Disability Status Scale; QD: quaque die = once-daily



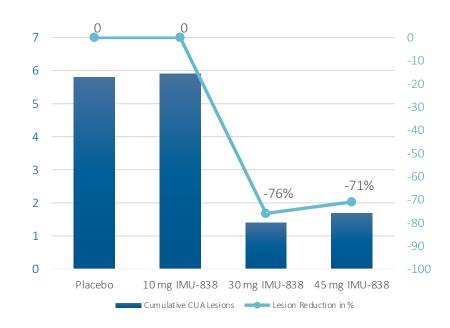


EMPhASIS Trial: Strong Reduction of MRI Lesion Activity Primary Endpoint Hit With High Significance, Pooled Cohorts 1 & 2

Vidofludimus Calcium Showed Strong Activity on Primary Study Endpoint in Phase 2 Trial

- Double-blind, placebo-controlled, randomized, parallelgroup phase 2 trial in RRMS
- Blinded main treatment period of 24 weeks
- Randomized 268 patients in 36 centers across four European countries
- Cohort 1: 30 and 45 mg or placebo
- Cohort 2: 10 mg or placebo
- Extended treatment period of up to 9.5 years to observe long-term safety is ongoing

Study endpoint: Reduction in cumulative CUA lesions up to week 24

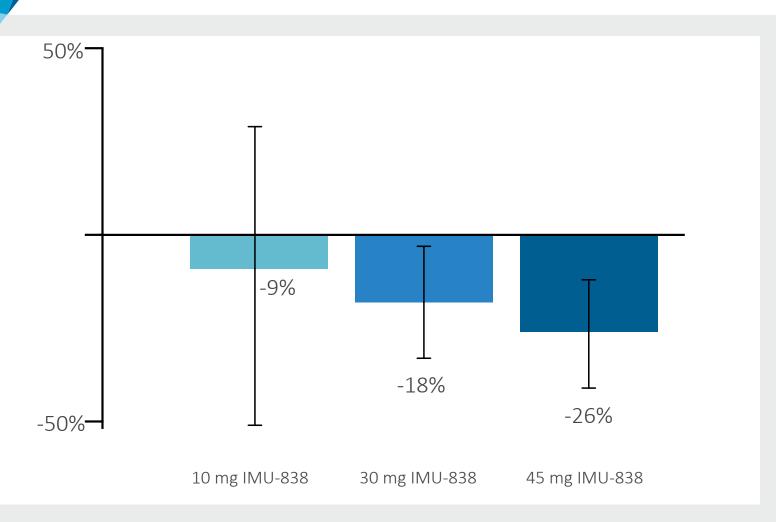


Primary and key secondary endpoints met with high statistical significance (primary: p = 0.0002 / key secondary: p < 0.0001)

As Cohort 2 only allowed MRI machines of 1.5T, pooled data of Cohorts 1 & 2 only include patients that were evaluated at MRI field strength of 1.5 Tesla. Modified full analysis set C1/C2 (N10 = 47, N30 = 65, N45 = 66, NPBO C1 = 59, NPBO C2 = 12) Data displayed are as adjusted mean values. Estimates are adjusted for baseline volume of T2 lesions and baseline number of Gd+ lesions (0, >=1) using a generalized linear model with a negative binomial distribution and a logarithmic link function. Log transformation of time from first investigational medicinal product (IMP) dose to date of last MRI assessment with non-missing values is used as offset term. RRMS: relapsing-remitting multiple sclerosis; MRI: magnetic resonance imaging; CUA: cumulative unique active, Gd+: gadolinium-enhancing



EMPhASIS Trial: Reduction of Serum NfL Concentrations Observed Versus Placebo After 24 Weeks, Pooled Cohorts 1 & 2



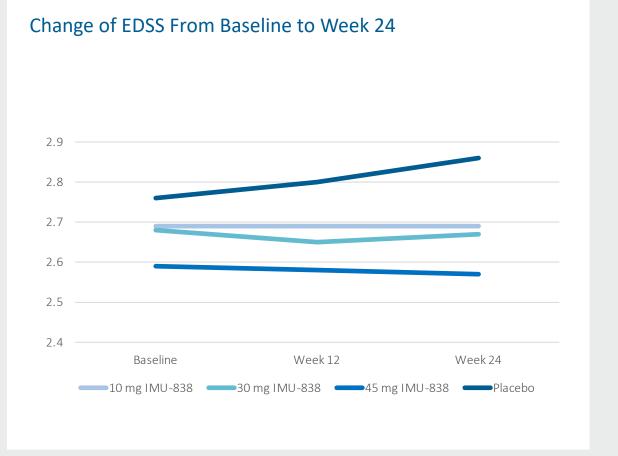
Vidofludimus calcium showed a remarkable reduction in NfL levels in all active doses tested compared with placebo

- The relative change of serum NfL versus placebo is proportional to vidofludimus calcium dose.
- Higher doses are expected to show stronger neuroprotective effects

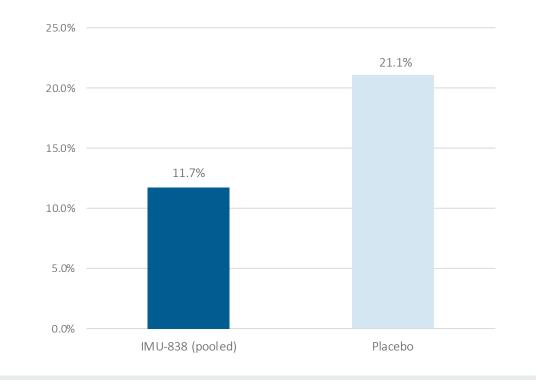
Displayed are median values of differences between percentage change of serum neurofilament light chain concentration (Hodges-Lehmann estimation), treatment vs. placebo, combined data for Cohort 1 and 2 patients; NfL: neurofilament light chain



EMPhASIS Trial: Longitudinal Change of EDSS and Unconfirmed EDSS Progressions (Pooled Cohorts 1 & 2)



Proportion of Patients With Unconfirmed EDSS Progression up to Week 24



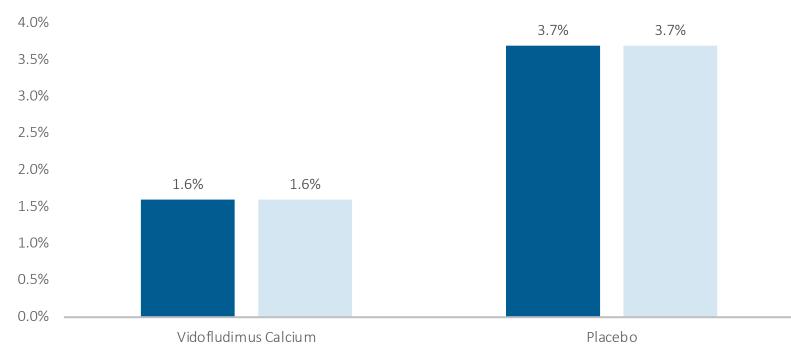
Displayed are mean values, combined data for Cohort 1 and 2 patients EDSS: Expanded Disability Status Scale



EMPhASIS Trial: Confirmed Disability Worsening Events End of 24-Week Blinded Treatment Period

CDW Events at the End of the 24-Week Blinded Treatment Period

■ 12-Week CDW ■ 24-Week CDW



Data confirm a signal in preventing 12-week and 24week confirmed disability worsening events as compared to placebo. Confirmatory data will be obtained in the phase 3 ENSURE clinical program.

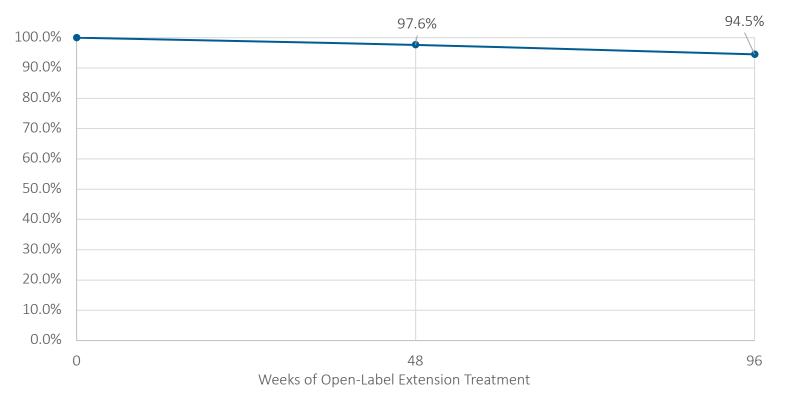
CDW: confirmed disability worsening; EDSS: Expanded Disability Status Scale

Only disability worsenings with a trigger point during the 24-wek blinded treatment period are considered. The EDSS increases during the blinded treatment phase were subsequently confirmed during open-label extension phase of the trial. Patients at risk in this analysis are 187 for vidofludimus calcium (pooling 10, 30 and 45 mg data) and 81 for placebo.

The trigger event is an EDSS progression defined as an increase in the EDSS compared to Baseline of at least 1.5 points if Baseline EDSS = 0, of at least 1.0 points if Baseline EDSS of 1-5, or of at least 0.5 points if Baseline EDSS \geq 5.5 12-week CDW: The confirmation event is at least 77 days after the trigger event. At the confirmation event and each assessment between trigger and possible confirmation event, EDSS must be at least as high as at the trigger event. 24-week CDW is are defined analogously, the only difference being the time interval between trigger event and confirmation visit, which is at least 161 days. Full analysis set pooled cohorts 1&2 (N10 = 47, N30 = 71, N45 = 69, NPBO C1 = 69, NPBO C2 = 12)

EMPhASIS Trial: Interim Analysis Regarding 24-Week CDW Events Patients Free of 24-Week CDW After 1 and 2 Years of OLE Vidofludimus Calcium Treatment

Proportion of Patients Free From 24-Week Confirmed Disability Worsening



Data confirm that only a few patients on continuous treatment with vidofludimus calcium develop 24-week confirmed CDW events over a 2-year time frame.

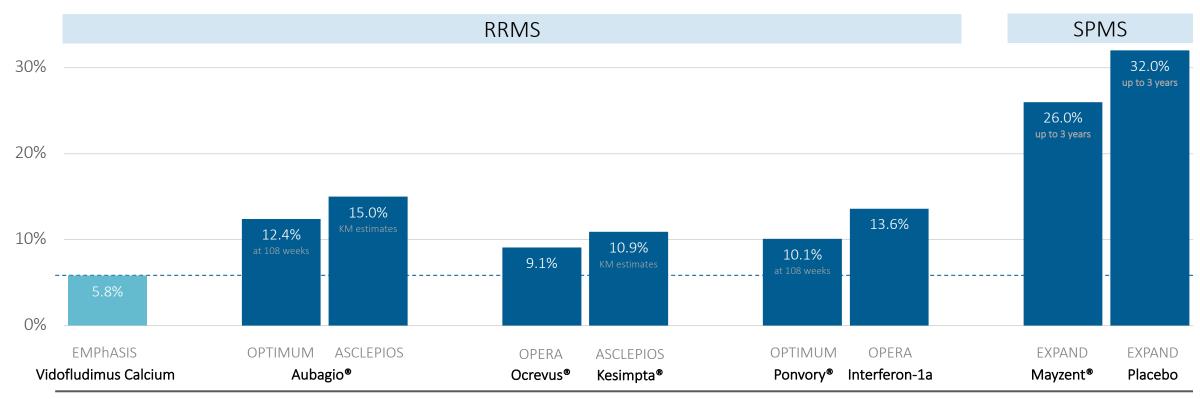
CDW: confirmed disability worsening; EDSS: Expanded Disability Status Scale

Only disability worsenings compared to start of extended treatment are considered. Patients at risk in this analysis are 223 at 48 weeks and 158 for 96 weeks. This includes all patients randomized to either placebo or any dose of vidofludimus calcium. After 24 week of blinded treatment, all patients continued with open-label treatment with either 30 mg or 45 mg vidofludimus calcium. Survival rates and times estimated by the Kaplan-Meier method. 95% CI for rates based on Greenwood's formula. The trigger event is an EDSS progression defined as an increase in the EDSS compared to Baseline of at least 1.5 points if Baseline EDSS = 0, of at least 1.0 points if Baseline EDSS of 1-5, or of at least 0.5 points if Baseline EDSS ≥ 5.5 24-week CDW: The confirmation event is at least 161 days after the trigger event. At the confirmation event and each assessment between trigger and possible confirmation event, EDSS must be at least as high as at the trigger event.



12-Week Confirmed Disease Worsening after 2 Years (96 Weeks) EMPhASIS Data from OLE Interim Analysis 2022 Compared to Examples from Historical Trials

Patients With 12-Week/3-Months Confirmed Disability Worsening (% of Patients at Risk)



The trigger event is any EDSS progression during the open-label extension (OLE) period defined as an increase in the EDSS compared to start of the OLE period (Baseline) of at least 1.5 points if Baseline EDSS = 0, of at least 1.0 points if Baseline EDSS of 1-5, or of at least 0.5 points if Baseline EDSS ≥ 5.5. Patients with RRMS at risk in this EMPhASIS analysis are 158 at 96 weeks. Data cut-off was Oct 16, 2022. This includes all patients randomized to either placebo or any dose of vidofludimus calcium during the 24-week blinded treatment period and then continued with open-label treatment with either 30 mg or 45 mg vidofludimus calcium. Survival rates and times estimated by the Kaplan-Meier method. 95% CI for rates based on Greenwood's formula.

12-week CDW: The confirmation event is at least 77 days after the trigger event. At the confirmation event and each assessment between trigger and possible confirmation event, EDSS must be at least as high as at the trigger event.

24-week CDW is are defined analogously, the only difference being the time interval between trigger event and confirmation visit, which is at least 161 days.

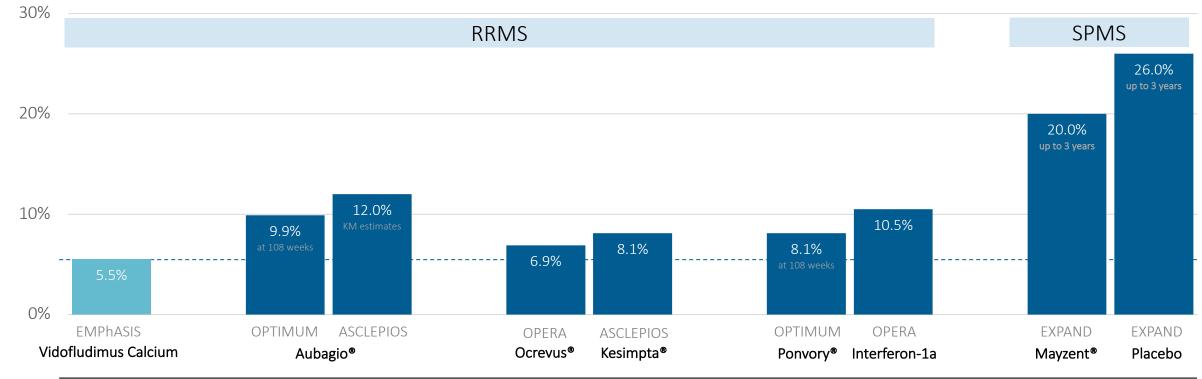
KM: graphical estimates from published Kaplan-Meier curves; EDSS: Expanded Disability Status Scale; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis. All trials performed in relapsing-remitting Multiple Sclerosis. Except EXPAND trial was performed in patients with active and non-active secondary progressive MS (SPMS).

Vidofludimus Calcium: Immunic data; OPTIMUM: Kappos et al. 2021; ASCLEPIOS: Hauser et al. 2020; EXPAND: Kappos et al. 2018; ULTIMATE: Steinman et al. 2022; OPERA: Hauser et al. 2017



24-Week Confirmed Disease Worsening after 2 Years (96 Weeks) EMPhASIS Data from OLE Interim Analysis 2022 Compared to Examples from Historical Trials

Patients With 24-Week/6-Months Confirmed Disability Worsening (% of Patients at Risk)



The trigger event is any EDSS progression during the open-label extension (OLE) period defined as an increase in the EDSS compared to start of the OLE period (Baseline) of at least 1.5 points if Baseline EDSS = 0, of at least 1.0 points if Baseline EDSS of 1-5, or of at least 0.5 points if Baseline EDSS ≥ 5.5. Patients with RRMS at risk in this EMPhASIS analysis are 158 at 96 weeks. Data cut-off was Oct 16, 2022. This includes all patients randomized to either placebo or any dose of vidofludimus calcium during the 24-week blinded treatment period and then continued with open-label treatment with either 30 mg or 45 mg vidofludimus calcium. Survival rates and times estimated by the Kaplan-Meier method. 95% CI for rates based on Greenwood's formula.

12-week CDW: The confirmation event is at least 77 days after the trigger event. At the confirmation event and each assessment between trigger and possible confirmation event, EDSS must be at least as high as at the trigger event.

24-week CDW is are defined analogously, the only difference being the time interval between trigger event and confirmation visit, which is at least 161 days.

KM: graphical estimates from published Kaplan-Meier curves; EDSS: Expanded Disability Status Scale; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis. All trials performed in relapsing-remitting Multiple Sclerosis. Except EXPAND trial was performed in patients with active and non-active secondary progressive MS (SPMS).

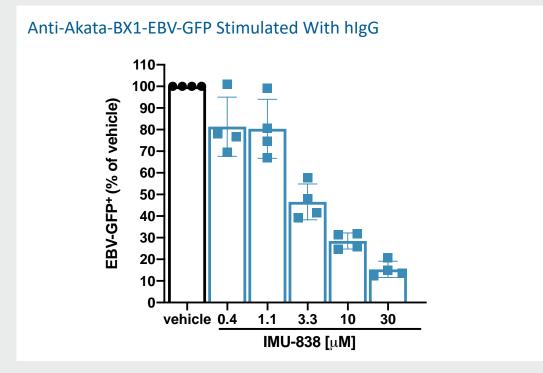
Vidofludimus Calcium: Immunic data; OPTIMUM: Kappos et al. 2021; ASCLEPIOS: Hauser et al. 2020; EXPAND: Kappos et al. 2018; ULTIMATE: Steinman et al. 2022; OPERA: Hauser et al. 2017



Vidofludimus Calcium: DHODH Inhibition Provides Broad-Spectrum Antiviral Activity Against Different Pathogenic Viruses



Vidofludimus Calcium Showed Concentration-Dependent Anti-EBV Activity



Left: Marschall et al., Poster ECTRIMS 2021 / Right: Eur J Clin Invest. 2020;50:e13366 EBV: Epstein-Barr Virus; IgG: immunoglobulin G



Vidofludimus Calcium Inhibits Epstein-Barr Virus (EBV) Replication and Reactivation

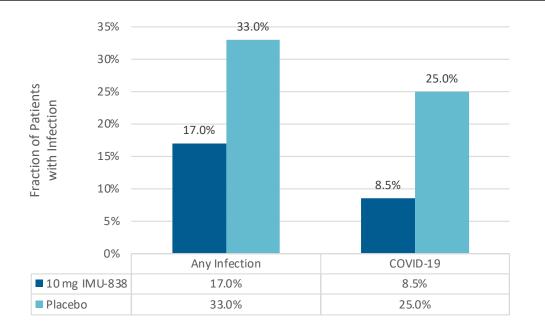
- Viruses rely on the host cell's infrastructure for replication
- Inhibition of DHODH by vidofludimus calcium leads to a depletion of pyrimidine nucleotides that are needed for the
 - Production of viral RNA and DNA (virus genome)
 - And Production of viral proteins (via mRNA)
- By targeting the host cell metabolism, vidofludimus calcium has shown to be active against different RNA and DNA viruses *in vitro* including strong anti-EBV activity



Vidofludimus Calcium Showed Interesting Hints for Clinical Anti-SARS-CoV-2 Activity and Maintaining Humoral Response



Treatment Corresponds With Decreased Number of Opportunistic SARS-CoV-2 Infections



Phase 2 EMPhASIS Trial in RRMS Number of reported COVID-19 cases in Cohort 2



Treatment Does Not Interfere With Antibody Development During SARS-CoV-2 Infection

	Day	v 6	Day	/ 14	Day 28		
	lgA	lgG	lgA	lgG	lgA	lgG	
Placebo	84%	88%	94%	94%	97%	99%	
Vidofludimus Calcium	86%	93%	97%	97%	95%	100%	

Phase 2 CALVID-1 Trial in COVID-19

Proportion of patients with anti-SARS-CoV-2 IgA or IgG antibodies

COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus; RRMS: relapsing-remitting multiple sclerosis; QD: quaque die = once-daily; IgA: immunoglobulin A; IgG: immunoglobulin G



Unrivaled Safety and Tolerability Profile Observed in Multiple Clinical Trials

- Safety profile similar to placebo: no general safety signals observed in clinical trials so far
- No increased rates of diarrhea, neutropenia, or alopecia
- No increased rates of infections and infestations or hematology values

- Drug exposure tested in more than 1,100 human subjects and patients, to date
- Low rates of adverse events
- No signals for hepatotoxicity or elevations of liver enzymes and no Hy's law cases observed



EMPhASIS Trial: No Signal for an Increase of Infections and Infestations

TEAE of SOC: Infections and Infestations	30 mg IMU-838	45 mg IMU-838	Placebo
Patients With TEAE	18.3%	23.2%	23.2%



EMPhASIS Trial: Absence of Hepatotoxicity Signals

Liver Enzyme Elevations	IMU-838 (30 mg and 45 mg pooled)	Placebo		
Number of Patients	140	69		
ALT or AST >5xULN	2.9% (4)	2.9% (2)		
ALT or AST >10xULN	0.7% (1)	1.4% (1)		
ALT or AST >15xULN	0.0% (0)	0.0% (0)		

TEAE: treatment-emergent adverse events; SOC: system organ class



Vidofludimus Calcium's Safety Profile to Date is Unique

	Vidofludimus Calcium ^[1]	Aubagio ^{® [2]}	Ocrevus ^{® [3]}	Tecfidera ^{® [4]}	Mavenclad ^{® [5]}	Gilenya ^{® [6]}	Mayzent ^{® [7]}	Zeposia ^{® [8]}
PML Risk	•		•	•	0		0	0
Increased Number of Infections	•		•	•	0	•	0	0
Vaccination Limitations	۲	۲	•	•	•	0	0	0
Gastrointestinal Toxicities, Incl. Diarrhea	۲	•	0	•	•	•	•	
Cardiovascular Risks, Incl. Blood Pressure		0			•	•	0	•
Lymphopenia	•	0	•	•	•	•	0	0
Neutropenia	•	•	•	•	•	0	0	0
Risk of Liver Injury	۲	!	0	•	•	•	0	0
Rebound Effect		۲		•	•	•	•	•
Increased Risk of Cancer	۲		•	•	ļ	0	0	0
Macular Edema	۲	۲		•		•	•	•
Favor	🔵 Favorable Profile 🛛 😑 Clinical Concern / Risk 🥥 Substantial Risk 📙 Black Box Warning 🔲 No data available							

This classification is based on Immunic's assumptions according to clinical trial results regarding likelihood and severity of risk as well as FDA labels of the drugs displayed: [1] https://www.immunic-therapeutics.com/2020/09/11/immunic-inc-publishes-full-unblinded-clinicaldata-from-phase-2-emphasis-trial-of-imu-838-in-patients-with-relapsing-remitting-multiple-sclerosis-and-announces-poster-presentation-at-the-msvirtual20/ [2] O'Connor et al., 2011 NEJM [3] oiajfoij. Hauser et al. 2017., NEJM, Montalban et al. 2017, NEJM [4] Gold et al., 2012 NEJM, Fox et al., 2012 NEJM [5] Giovannoni et al., 2010 NEJM [6] Kappos et al., 2010 NEJM, Cohen et al., 2010 NEJM [7] Kappos et al 2018 Lancet [8] Comi et al., 2020 Lancet



EMPhASIS Trial: Patients Feel Well-Treated With Vidofludimus Calcium



Reflected in Low Discontinuation Rates for Vidofludimus Calcium-Treated RRMS Patients, Considerably Lower Than Placebo*

	Vidofludimus Calcium	Glatiramer Acetate ^[1]	Aubagio [®] [2]	Tecfidera [®] [3]	Gilenya [®] [4]	Zeposia [®] [5]
Administration	Oral	Injectable	Oral	Oral	Oral	Oral
Daily Dose	30 mg QD	20 mg QD	14 mg QD	240 mg TID	1.25 mg QD	1 mg QD
Treatment Period	24 weeks	9 months	36 weeks	24 weeks	6 months	24 weeks
Active Treatment	2.8%	5.9%	19.3%	15.6%	5.4%	2.2%
Placebo	7.2%	5.8%	6.6%	9.2%	6.5%	3.3%

*The table summarizes the data on treatment/study discontinuation rates of the commercial dose in phase 2 trials of RRMS drugs. If the commercial dose was not included in the phase 2 trials, the dose closest to the commercial dose was shown. This high-level comparison is provided for illustrative purposes only, is based on publicly available data and does not purport to be a comprehensive comparison or depiction of the other trials. Larger data sets than presented in this presentation are publicly available for certain of the compounds included on this slide. Please note that these results are taken from placebo-controlled trials, and these medications have not been tested in head-to-head assessments.

[1] Comi et al. Ann Neurol. 2001;49(3):290-297 [2] O'Connor et al. *Neurology*. 2006;66(6):894-900 [3] Kappos et al. Lancet. 2008;372(9648):1463-1472 [4] Kappos et al. N Engl J Med. 2006;355(11):1124-1140 [5] Cohen JA, Arnold DL, Comi G, et al. Lancet Neurol. 2016;15(4):373-381 QD: quaque die = once-daily; TID: ter in die = three times daily; RRMS: relapsing-remitting multiple sclerosis



Vidofludimus Calcium: IP Position

Vidofludimus Calcium is Protected by Several Layers of Patents:





Patent on the specific salt form and pharmaceutical composition of vidofludimus calcium, granted in the United States, Europe and other key markets – expires in 2031



New patent filed in 2017 on the dosing regimen protecting the applied dosing scheme of the ongoing and planned therapeutic studies – expires in 2038, if granted



New patent filed in 2018 on the specific polymorph of vidofludimus calcium used in current studies – expires in 2039, if granted



New patent filed in 2020 on vidofludimus calcium's antiviral activity for use in COVID-19 – expires in 2041, if granted



Another level of protection can be expected by data exclusivity in the United States and in Europe based on vidofludimus calcium's classification as a New Chemical Entity (NCE)



Vidofludimus Calcium Targeted to Elevate the Standard of Care With a Holistic Solution for the Full Spectrum of MS Patients

Phase 3 program of vidofludimus calcium in RMS ongoing based on excellent clinical data package	 Strong effect on all relevant endpoints in 268 RRMS patients, including anti-inflammatory & neuroprotective effects Unrivaled safety, to date, with over 1,100 individuals treated
New third-party data clearly highlights the unmet need of preventing disability progression , with relapse-independent disease progression being dominant even in early RRMS	 The understanding of MS has evolved, with evidence showing a smoldering disease that is connected to Epstein-Barr virus and subsequent inflammation & neurodegeneration
Vidofludimus calcium selectively manages all three components needed to quell smoldering MS	 Anti-viral effect Anti-inflammatory effect Neuroprotective impacts
Large market opportunity exists for a therapy that can holistically and sustainably address patients' needs	Even current market leaders only optimize for one featureCurrent treatment options have serious tolerability downsides



IMU-935: A Potentially Best-in-Class Oral IL-17 Inhibitor

Uniquely Acting and Highly Selective RORγt Inverse Agonist

Clear Need for Potent and Specific Inhibition of IL-17 in Multiple Autoimmune Diseases

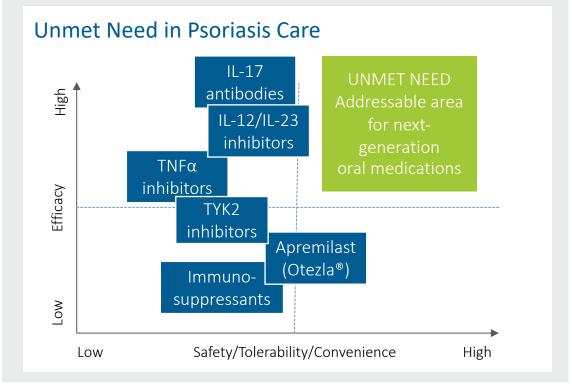


IL-17 is Significant in Many Autoimmune Diseases

- Imbalance between regulatory T cells (T_{regs}) and Th17 cells contributes to autoimmune diseases, with Th17 cells secreting proinflammatory cytokines such as IL-17^[1]
- RORγt is a master regulator of Th17 development and expression of IL-17^[2]
- Multiple diseases are driven by IL-17; many represent significant market opportunities^[3]:
 - Psoriasis (USD 18 billion)
 - Psoriatic arthritis (USD 7 billion)
 - Rheumatoid arthritis (USD 32 billion)



Goal: Develop a Potent, Specific, and Orally Available IL-17 Inhibitor

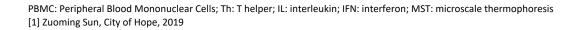


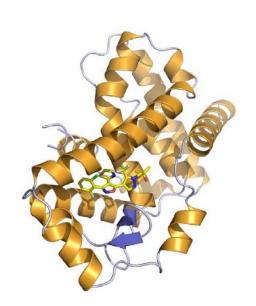
[1] Fasching, Patrizia, et al. Molecules 2017 22.1: 134 [2] Bassolas-Molina, Helena et.al., Front. Immunol., 22 October 2018 [3] DRG Clarivate 2020 G7 Markets Th: T helper; IL: interleukin; TNF: tumor necrosis factor; TYK2: Tyrosine kinase 2; RORy: retinoic acid receptor-related orphan nuclear receptor gamma

IMU-935 Inhibits Cytokines Associated With Autoimmune Diseases With an IC₅₀ of 3-5 nM in Stimulated Human Lymphocytes

	IC ₅₀ (μM)
IL-17A	0.005
IL-17F	0.004
IFNγ	0.003
IL-1a and b	no inhibition
IL-4,5,6,8	no inhibition
RORγ (MST)	0.024
RORγ (cellular, reporter assay)	0.020
Th17 differentiation (murine) ^[1]	0.135

Readout: effect on cytokine production after 48 hours in PBMC

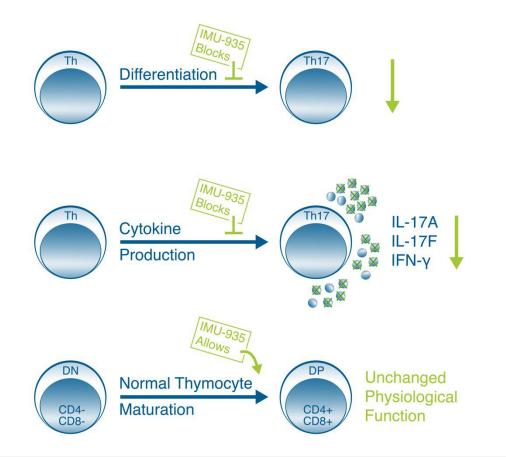




Co-crystal structure (Resolution 2.6 A) of a closely related derivative compound binds to hydroxycholesterol binding site of RORy



IMU-935 Selectively Inhibits Th17 Differentiation and IL-17 Secretion





The differentiation towards Th17 cells is inhibited by IMU-935



The production of IL-17A and IL-17F is inhibited by IMU-935



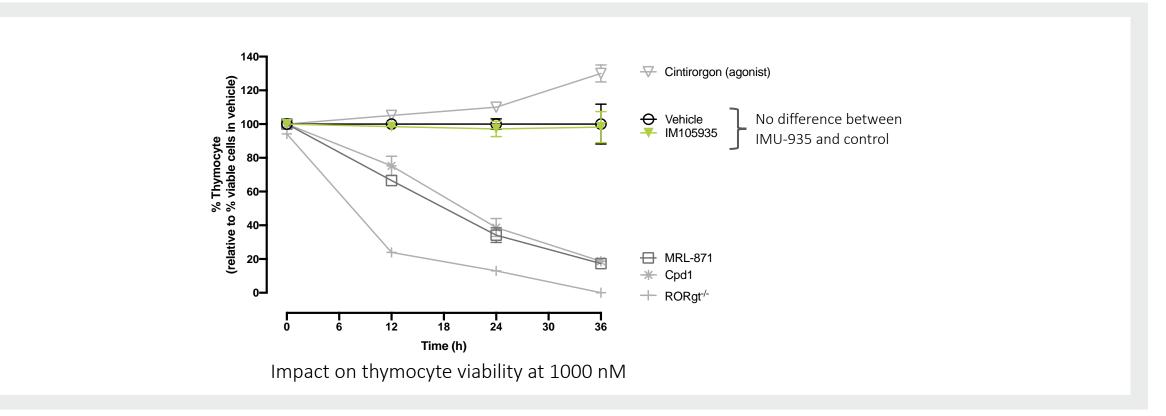
The physiological maturation of T cells within the thymus is not affected by IMU-935

Th: T helper; IL: interleukin; IFN: interferon; DN: double-negative; DP: double-positive; CD: cluster of differentiation



IMU-935 Does Not Induce Thymocyte Apoptosis

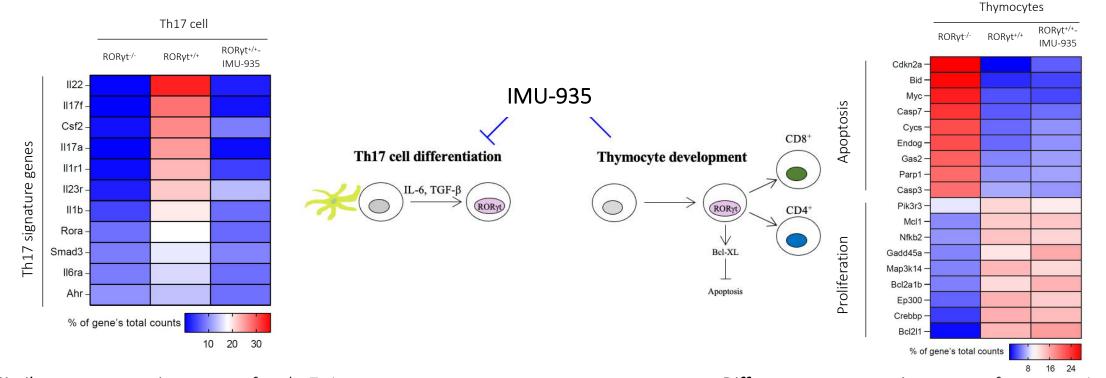
In Contrast to IMU-935, Comparator Compounds Have a Negative Impact on Thymocyte Viability and Therefore Bear the Risk of Lymphoma.



Sun, Zuoming. City of Hope, 2021, unpublished



IMU-935 Blocks Th17 Differentiation But Allows Normal Thymocyte Maturation: Gene Expression Profiles



Similar gene expression pattern for Th17 signature genes in RORyt knockout and wild type cells treated with IMU-935 Different gene expression pattern for apoptosis and proliferation signature genes in RORγ knockout and IMU-935 treatment, but similar for RORγ+/+

Zuoming Sun, City of Hope, 2021

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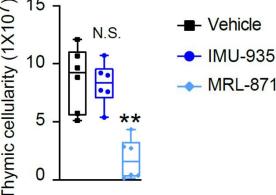


IMU-935 Allows Normal Thymocyte Maturation In Vivo Acute Model, 3 Days of Treatment

IMU-935 (100 mg/kg BID), and MRL-871 (100 mg/kg BID) were tested for 3 days in C57BL/6j mice



Guo et al., 2016, Cell Reports (MRL-871), Guntermann et al., 2017, JCI Insight (Cpd1), Mahalingam et al., 2019, Clin Cancer Res. (Cintirorgon) Sun, Zuoming. City of Hope, 2021, unpublished



In contrast to MRL-871, IMU-935 does not impact thymus size, thymocyte cell numbers or thymocyte maturation in an acute mouse model.



Phase 1 Clinical Trial: Trial Design and Current Status





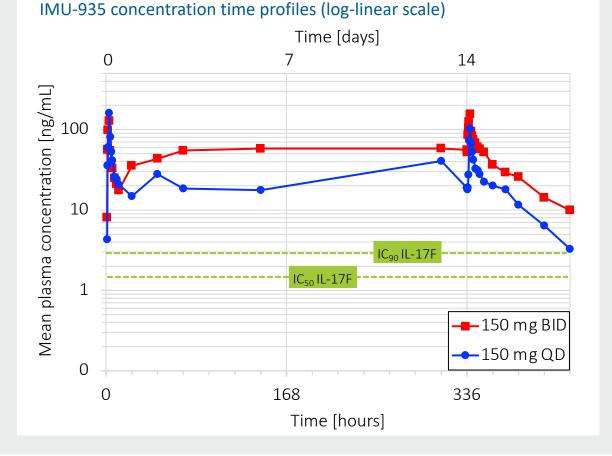


Evaluation of	Evaluation of	Evaluation of
single ascending doses (SAD)	multiple ascending doses (MAD)	moderate-to-severe psoriasis
Healthy human subjects	Healthy human subjects	patients receiving 28-day
randomized to receive single	randomized to receive 14-day	treatment of
dose of IMU-935 or placebo	treatment of IMU-935 or placebo	IMU-935 or placebo
 Dose escalation completed: 100, 200, 300 and 400 mg of IMU-935 79 subjects enrolled IMU-935 was well-tolerated and showed dose-linear PK 	 Dose escalation completed: 150 mg QD and 150 mg BID of IMU-935 15 subjects enrolled IMU-935 was well-tolerated and steady- state was achieved after 3-6 days of dosing 	 150 mg QD and 150 mg BID of IMU-935 41 patients enrolled Detailed evaluation of group-level interim analysis ongoing Overall trial ongoing and blinded

Immunic

PK: pharmacokinetic; QD: quaque die = once-daily; BID: bis in die = two times daily

Phase 1 Clinical Trial: Pharmacokinetic Results Part B: Summary of QD and BID Dosing Regimen for IMU-935



F S

Favorable PK Properties for IMU-935 atSteady-State Observed

Pharmacokinetic parameters in steady-state (mean)	150 mg QD	150 mg BID	
C _{max, ss} (ng/mL)	124	206	
C _{min, ss} (ng/mL)	15.7	48.5	
T _{max, ss} (hr)	2.8	2.4	
t _{1/2, ss} (hr)	29.0	38.0	
AUC _{last} (hr*ng/mL)	1540	3040	

Ion-compartmental analysis

- Fast achievement of steady-state within first week and stable steady-state trough levels over 14-day treatment period.
- Accumulation factors of 1.29 (150 mg QD) and 2.21 (150 mg BID) allowing predictable trough levels.

Interim data, PK analysis ongoing

QD: quaque die = once-daily; BID: bis in die = two times daily; PK: pharmacokinetic; ss: steady-state; C_{max}: maximum plasma drug concentration; T_{max}: time to reach maximum plasma concentration; hr: hours; t_{1/2}: half-life; AUC_{last}: area under the concentration-time curve from dosing to last measurement Accumulation factors were calculated as the relationship of AUC_{0-tau} of Day 14/Day 1 (after first dosing).



Phase 1 Clinical Trial: Summary of Safety and Tolerability Findings Part B



Daily Dosing of IMU-935 in Healthy Human Subjects Over 14 Days Was Found to Have a Favorable Safety and Tolerability Profile



No serious adverse events



No dose-dependency in adverse events



No maximum tolerated dose reached



No trends for post-dose changes in any laboratory parameter



No adverse events regarding any laboratory parameter



No medically relevant changes in vital signs or 12-lead electrocardiograms as compared to placebo



IMU-935 Phase 1 Clinical Trial Part C in Moderate-to-Severe Psoriasis Patients



Identifying Therapeutic Activity of IMU-935 in Moderate-to-Severe Psoriasis Patients

- 28-day double-blind, placebo-controlled dose escalation trial to evaluate safety, tolerability, pharmacodynamics, pharmacokinetics and exploratory efficacy of IMU-935 in patients with moderate-to-severe psoriasis
- Initial two dose cohorts of 150 mg QD and 150 mg BID of IMU-935 did not yet achieve clinical proof-of-concept
 - Group-level interim analysis revealed unexpected high placebo rate; two active arms did not separate from placebo at four weeks
 - Overall trial is ongoing and remains blinded
 - Although safety data also remains blinded, administration of IMU-935 and placebo were safe and well-tolerated, no new safety signals observed
 - Immunic expects to continue IMU-935 development in psoriasis and will determine next steps for the program
 - Immunic plans to provide further updates and guidance on potential next steps in Q1/2023

QD: quaque die = once-daily; BID: bis in die = two times daily



IMU-935 As Treatment Option in Castration-Resistant Prostate Cancer Targeting Key Resistance Mechanism

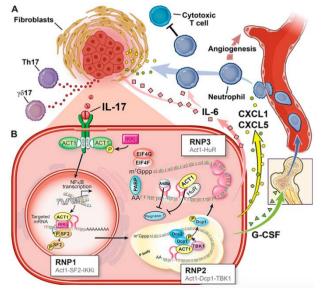


Inhibition of RORy

- The androgen-receptor mutant variant AR-V7 lacks the ligandbinding domain – which is the target of enzalutamide and abiraterone – and remains constitutively active as a transcription factor.
- IMU-935 represses the mutated androgen receptor AR-V7 expression – and subsequent target genes.



- IL-17 contributes to the formation, growth and metastasis of cancers.
 - Induces mitogenic signaling



AR-V7: androgen receptor variant 7/mutated form; MDSC: myeloid-derived suppressor cells; APC: antigen presenting cells; Th: T helper; IL: interleukin [1] Strauss et al., Cellular & Molecular Immunology (2021); Illustration: Zhao, J., Chen, X., Herjan, T., Li, X.; J Exp Med 6 January 2020; 217 (1): e20190297



RORγ in Myeloid-Derived Suppressor Cells

- Myeloid-specific expression of RORy marks advanced cancer inflammation.
- Expansion of circulating RORy+ myeloid cells is associated with an increased number of MDSCs.
 Inhibition of RORy in myeloid cells reprograms cancer myelopoiesis in favor of effector APCs with antitumoral effects.^[1]
- IL-17 mediates the induction, recruitment and expansion of MDSCs.



Phase 1 Clinical Trial of IMU-935 in CRPC NCT05124795

Open-Label Dose Escalation Trial to Evaluate Safety, Tolerability, Anti-Tumor Activity, and Pharmacokinetics of IMU-935 in Patients With Progressive, Metastatic CRPC

- Main treatment will be single agent IMU-935 for 3 cycles of 28 days each
- Dose escalation follows a Bayesian optimal interval (BOIN) design
- An expansion cohort can be added at a therapeutically active dose level
- Patients who benefit can receive extended treatment
- At each dose level:
 - A safety analysis after 28 days will be performed to consider start of next dose
 - An interim activity analysis after 3 months of treatment will be performed
 - A main cohort analysis will be performed when the last patient in treatment reaches the 6 months follow-up visit
- Initial safety data available show a promising safety profile, with only benign adverse events and no dose limiting toxicities
- More comprehensive update on safety and potential signs of anti-tumor activity is planned to be provided as soon as data from the dose expansion part are available



Principal Investigator

Johann Sebastian de Bono, M.D., Ph.D.

Regius Professor of Cancer Research and Professor in Experimental Cancer Medicine

The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust

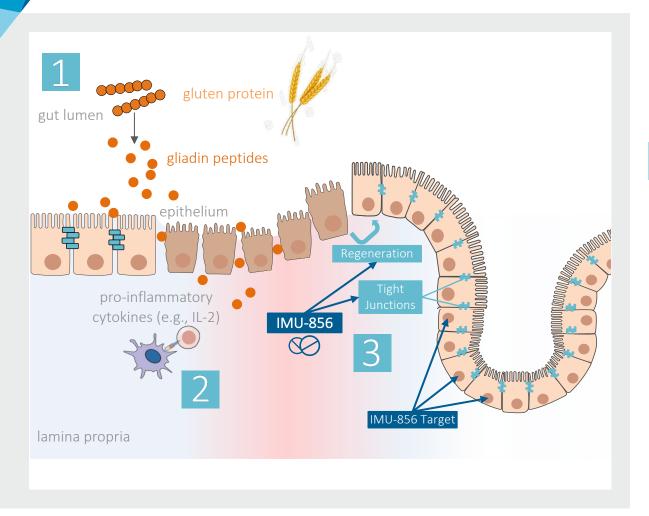
London, United Kingdom



IMU-856

Restoring Intestinal Barrier Function

Celiac Disease is a Serious Autoimmune Disease



Celiac disease is a multifactorial, complex **autoimmune disease** caused by an immune reaction against a degradation product of gluten and is strongly associated with **specific HLA class II gene variants (HLA-DQ2 and -DQ8)**^[1]

- Gluten is degraded into gliadin peptides which are taken up by the bowel epithelium (trans- or paracellular)
- In patients with a specific HLA protein (DQ2 and DQ8) composition, deaminated gliadin (by TG2) is recognized and can trigger an immune response which leads upon continued gliadin uptake to
 - ✓ Increased intestinal permeability
 - Epithelial and mucosal damage with negative changes of the gut architecture, including villous atrophy leading to malabsorption of nutrients
- Hypothesis for IMU-856's mode of action:

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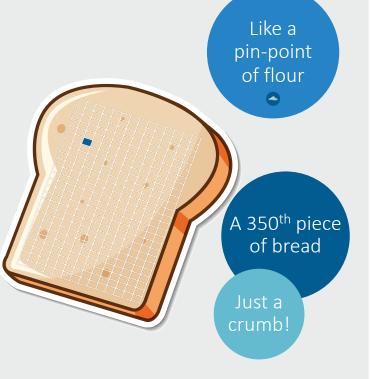
- Improves intestinal barrier function and restores permeability
- Restores villous architecture by triggering regenerative processes of the epithelial lining



HLA: human leukocyte antigen; TG2: tissue transglutaminase 2 Picture: self-drawn; [1] Caio et al. BMC Medicine (2019) 17:142

Celiac Disease Currently Has No Adequate Treatment Options

How much is 10 mg of gluten?



10 mg of gluten is the total limit for all foods combined for the entire day.



- The only established therapeutic option is a life-long strict adherence to a gluten free diet, which involves complete avoidance of proteins from wheat, barley, and rye.
- There is a high risk of accidental and inadvertent gluten intake, often due to a wide gluten cross contamination.
- A threshold of 10 mg gluten/day^[1] is considered safe for patients with celiac disease.



Symptomatic Patients Despite Gluten Free Diet

- Between 24% and 47% of patients show signs and symptoms of ongoing active celiac disease despite strict gluten free diet^[2], most likely due to:
 - Continuous (inadvertent) gluten exposure
 - Slow response to gluten withdrawal
- These patients are the main target for celiac disease medications.

Picture and Ref [1]: https://nationalceliac.org/celiac-disease-questions/understanding-gluten-levels/; [2] Lebwohl et al., Aliment Pharmacol Ther. 2014 March ; 39(5): 488–495



Patients Across the Spectrum of Celiac Disease Need Access to a Drug Treatment to Address Persistent Disease Activity Despite GFD

Patients With Celiac Disease Are Often Wrongly Diagnosed in Early Stages, Leading to Poorer Prognosis on Gluten Free Diet

Active Celiac Disease

- Numerous, intense gastrointestinal symptoms
- Antibody stimulation in response to gluten / gliadin
- >12 months for antibody normalization if GFD effective
- Histologic remission possible in 1-2 years

Treatments available

Gluten Free Diet (GFD)

Persistent Villous Atrophy

- Marked by enterocyte atrophy (barrier fully compromised)
- Often seen in 25-50% of patients, despite long-term GFD

Maintaining GFD

Histologic recovery rare

Refractory Disease

- Persistent malabsorption and associated comorbidities, persistent villous atrophy
- High mortality due to lymphoma

Immunosuppression

Benjamin Lebwohl, Sanders, and Green 2018; B. Lebwohl et al. 2014; Caio et al. 2019; Nasr et al. 2016 GFD: gluten free diet



Phase 1 Clinical Trial: Trial Design and Current Status







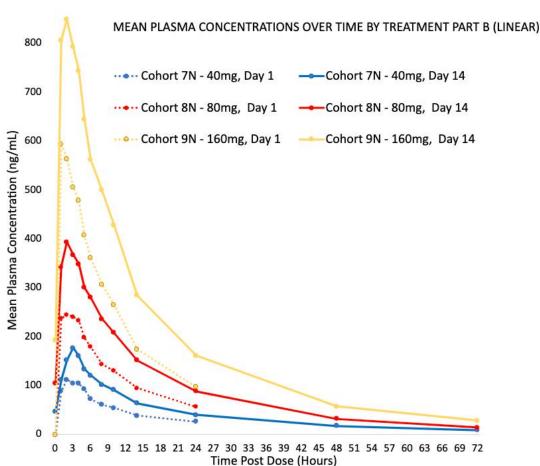
Evaluation of	Evaluation of	Evaluation of
single ascending doses (SAD)	multiple ascending doses (MAD)	patients with celiac disease
Healthy human subjects	Healthy human subjects	receiving 28-day
randomized to receive single	randomized to receive 14-day	treatment of
dose of IMU-856 or placebo	treatment of IMU-856 or placebo	IMU-856 or placebo
 Planned dose escalation completed: 10, 20, 40, 80, 120 and 160 mg of IMU-856 45 subjects enrolled (IMU-856: n=33) IMU-856 was well-tolerated and showed dose-linear pharmacokinetics 	 Planned dose escalation completed: 40, 80 and 160 mg QD of IMU-856 26 subjects enrolled (IMU-856: n= 19) IMU-856 was well-tolerated and steady- state trough levels were achieved within first week of dosing 	 Dosing: 80 and 160 mg QD of IMU-856 Approximately 42 patients are planned to be enrolled Currently ongoing and actively recruiting; initial data expected in 2023



QD: quaque die = once-daily;

Dose-Linear Pharmacokinetics in Multiple Dosing (Day 1 and 14) Part B





- Terminal plasma half-life at steady state (Day 14 values) 17 to 21 hours comparable to single dose
- Linear pharmacokinetics also after multiple dosing with doseproportional increase in plasma C_{max} and AUC
- Accumulation factor of ~ 1.5 allowing predictable trough levels and drug exposure after once-daily oral administration

Value (mean)	Day 1		Day 14, steady state			
	Cohort 7N 40 mg	Cohort 8N 80 mg	Cohort 9N 160 mg	Cohort 7N 40 mg	Cohort 8N 80 mg	Cohort 9N 160 mg
C _{max} (ng/mL)	131	269	653	184	400	913
T _{max} (h)	2.40	2.20	1.83	3.00	2.65	2.17
T _{1/2} (h)	10.8	10.5	8.9	21.5	17.7	17.4
AUC _{0-tau} (h*ng/mL)	1300	3048	6190	2067	4829	9853

Cmax: maximum plasma drug concentration; h: hours; Tmax: time to reach maximum plasma concentration; T1/2 (h): terminal elimination half-life; AUC0-tau: area under the drug concentration-time curve from time zero to 24 hours



Multiple Doses of IMU-856 in Healthy Human Subjects Found to Have a Favorable Safety and Tolerability Profile



No IMP-related serious adverse events



No dose-dependency in adverse events



No maximum tolerated dose reached



No trends for post-dose changes in any laboratory parameter



No medically relevant changes in vital signs, physical examination or 12-lead electrocardiograms as compared to placebo



Pharmacokinetics well suited for once-daily administration and stable predictable trough levels

IMP: Investigational Medicinal Product



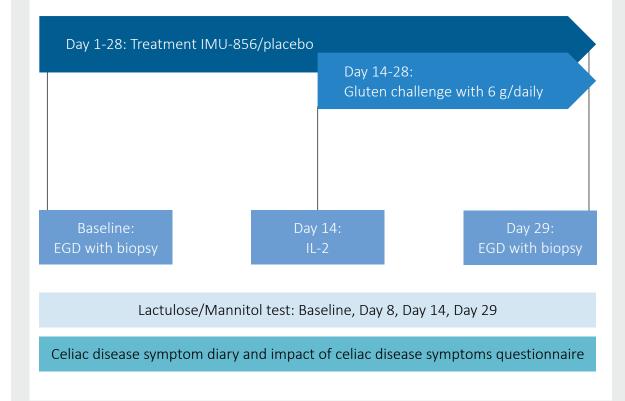
Phase 1 Clinical Trial of IMU-856 Part C in Celiac Disease Patients

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Proof-of-Concept Study

- Part C includes a well-controlled celiac disease patient population, designed to assess safety and tolerability of IMU-856 as well as pharmacokinetics
- Study measures acute disease marker change of serum IL-2 levels after first challenge with gluten
- Further assessment includes chronic disease markers (Vh:CrD) and PRO
- Performed at sites in Australia and New Zealand

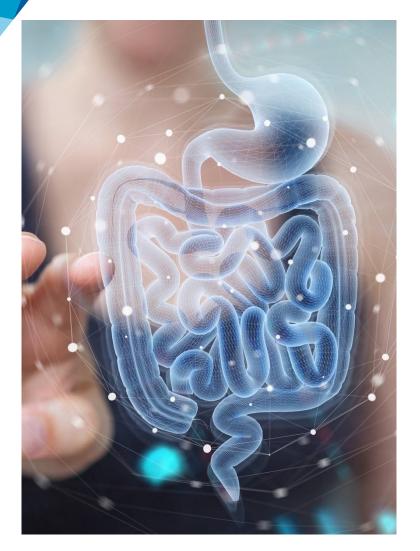
Flow Chart of Part C in Celiac Disease



EGD: esophagogastroduodenoscopy, VH:CrD: villous hight to crypt depth ratio, one of the main histological assessments of small bowel architecture, IL-2: interleukin-2



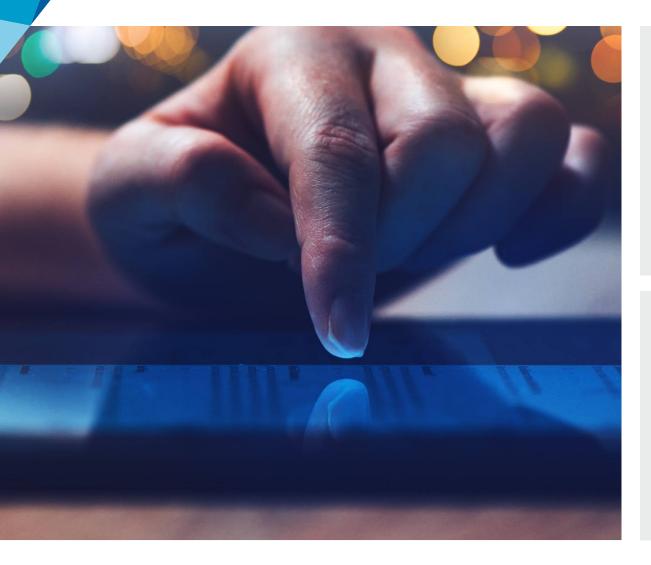
IMU-856: Favorable Phase 1 Safety, Tolerability and Pharmacokinetic Profile



- IMU-856 showed a favorable safety, tolerability and pharmacokinetic profile in the single and multiple ascending dose portions of the phase 1 clinical trial in healthy human subjects with no IMP-related serious adverse events.
- IMU-856 was safe and well-tolerated in single and 14-day repeated oral dosing in healthy human subjects. No maximum tolerated dose was reached and the investigated doses are expected to exceed the required therapeutic dosing of IMU-856.
- IMU-856 is currently being tested in a third portion of the phase 1 clinical trial in patients with celiac disease – setting the stage for a potential first-in-class oral celiac disease therapy.
- IMU-856 may offer extensive potential beyond celiac disease in other autoimmune diseases.



IMU-856: Anticipated News Flow



Celiac Disease R&D Webcast February 9, 2023

"Treatment of Celiac Disease: Current Challenges for Drug Development and Persistent Disease Activity Despite Gluten-Free Diet as the Unmet Medical Need"



Initial Phase 1b Celiac Disease Data of IMU-856 Expected in 2023



Immunic Therapeutics

Summary

Summary: Three Differentiated Programs in Clinical Development



Advanced clinical pipeline:

three differentiated investigational medicines in various phases of clinical development



Oral IL-17 inhibitor IMU-935:

huge potential in psoriasis and beyond; additionally being tested in CRPC patients



RMS phase 3 program of vidofludimus calcium ongoing, intended to provide a straightforward path towards regulatory approval



IMU-856 for intestinal barrier function: proof-of-concept trial in celiac disease ongoing; initial data expected in 2023



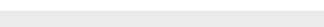
PMS phase 2 trial of vidofludimus calcium ongoing, designed to corroborate vidofludimus calcium's neuroprotective potential



Cash runway into Q4/2024

Cash position: USD 72.8 million (as of Sep 30, 2022) plus USD 56.4 million raised in Oct 2022

Shares outstanding: 39,261,547 (as of Oct 28, 2022)*



* Does not include 5,096,552 of preferred warrants from the company's October 2022 PIPE financing.



Summary: Several Clinical Data Readouts Expected in 2023



Celiac Disease R&D Webcast on February 9, 2023 IMU-856 Initial Phase 1b Celiac Disease Data in 2023

> Interim Analysis of Phase 2 CALLIPER Trial in PMS Estimated for H2/2023

IMU-935

IMU-838

Update and Guidance on Potential Next Steps for Phase 1 Trial in Psoriasis in Q1/2023



Thank You!



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