

Immunic Therapeutics Developing Selective Oral Therapies in Immunology

NASDAQ: IMUX | February 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.

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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







Singh General Counsel



Joerg Neermann, PhD Independent Director







Daniel Vitt, PhD CEO & President of

Immunic



Board of Directors

Renowned International

Tamar CFA Director

Maria Törnsén Director





Andreas

Hella Kohlhof, PhD CSO

Howson, Independent



Independent

Inderpal

Advanced Clinical Pipeline

Three Differentiated Programs in Various Phases of Clinical Development

Program	Target	Preclinical	Phase 1	Phase 2	Phase 3	Key Milestones
Vidofludimus		Relapsing Multiple Scle	erosis (RMS) – ENSURE T	rials		 Initial phase 1b celiac disease data of IMU-856 expected in mid-2023
Calcium (IMU-838)	DHODH	Progressive Multiple So	clerosis (PMS) – CALLIPE	R Trial		 Interim analysis of CALLIPER trial in PMS planned after half of the patients completed 24 weeks of treatment, estimated for H2/2023
Izumerogant (IMU-935)	IL-17 / RORγt	Psoriasis				 Interim analysis of first ENSURE trial in RMS planned after approximately half of the events occurred, estimated for late 2024
		Castration-Resistant Pr	ostate Cancer (CRPC)			 CALLIPER trial estimated to readout end
	Intestinal					of 2024
IIVIU-856	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



Vidofludimus calcium has the potential to be the leading treatment choice for all patients not choosing anti-CD20 therapy

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	REPORT	5	Article			
	Cite as: K. Biomerik et al. Science	80	Clonally expa	nded B cel	ls in multiple	
	10.1126/science.abj8222 (2022	£1	sclerosis bind	EBV EBNA	1 and GlialCAM	
ongitudinal analysis revea	ls high prevalence of					
pstein-Barr virus associat	ed with multiple sclerosis		https://doi.org/20.2028/s41586-022-04432	7 Tobias V. Lanu ^(3,1) , R. Cami	Be Drawer", Pessy P. No", Jae Seure Moor", Kevin M. Aste",	
jetil Bjornevik'†, Marianna Cortese'†, Brian C. He tenhen J. Elledre", David W. Niehuhr", Ann I. Sch	aly ^{4,5,5} , Jens Kuhle ⁴ , Michael J. Mina ^{4,5,6} , Yumei Leng ⁴ , er ⁶ , Kassandra L. Munter ¹ , Alberto Ascherio ^(20,0) , ²		Received: 6 August 2021 Accepted: 14 January 2022	Daniel Fernandez ² , Ricardi Christopher M. Bartley ⁶ , R Manael tyer ⁴ , J. Bradley Zu	o A. Fernandos ⁴ , Alojandro M. Gernat ¹⁴ , Gabriel Statan Nadj ¹⁴ , yan D. Schubert ⁴ , Isobel A. Howes ⁴ , Sara E. Viziquez ⁴⁰ , chero ¹⁴ , Bianca Teogen ⁴ , Jeffrey E. Dunn ¹⁰ , Chrintopher B. Lock ¹⁰ ,	
pend J. Lakeger, Davie W. Nicebauer, Alm J. Scherr, Assaulter J. Munger T, Alberto Ascherto "" " " " " " " " " " " " " " " " " " "		Published online: 24 January 2022	Lucas B. Kipp ¹⁰ , Victoria C. Mark S. Anderson ¹⁰ , Joseph Michael Platten ¹¹³⁰ , K. Ch	Cethani ¹⁴⁴ , Beatris M. Ueberheide ¹⁴⁴ , Blabe T. Ahab ¹⁴ , h L. Defile ¹⁴⁴ , Michael R. Wilson ² , Richael J. M. Bashford Rogara ¹⁴ , rintopher Garcia ⁴ , Lawrence Steinman ² & William H. Bobinson ¹⁴¹¹		
Remon Onion MA, USA. Centre for Community Nome Templan Programs. Depart Chan School of Public Health. Boston MA, USA. "Department of Pathology 5 reventive Neticine and Bostatistics, Unitor read Services University of the He Public Health. Biodan MJ, USA. "Channes Learnary Commonly of the He	per setupion microan experimente o submissi, anto regigna en viciogo, anto seguina interest of Epidemissiogo, and Department et in hermiciogo and Infectiona Busenese. Nancent T. Nigham and Women's Hospital. Hanvard Medical'School: Boston, MA. USA. "Department of alth Sciences, Bettenda, MAI, USA. "Department of Epidemissiogo, Harvard T. H. Cham'School con- Binshimm of Women's Hospital. and Hisman Michael School: Binshim MAI SA.			Multiple sclerosis (MS) autoreactive lymphocyt B.brunbocytes in the ce	is a heterogenous autoimmune disease in which tes attack the myelin sheath of the central nervous system, reproving that (CSF) of narient swith MS contribute to	
These authors contributed equally to this work.		Dowod		inflammation and secre	te oligoclonal immunoglobulins ¹³ . Epstein-Barr virus (EBV)	
hese authors contributed equally to this work.		lunded		remains unclear ¹ . Here's	emiologically linked to MS, but its pathological role we demonstrate high affinity molecular mirricry between	
Composing author, Email asschernlinigh harvard edu	demolication disease of the control persons sustem of	Itee		the EBV transcription fa	ctor EBV nuclear antigen 1 (EBNAI) and the central nervous	
inknown etiology. We tested the hypothesis that	MS is caused by Epstein-Barr virus (EBV) in a cohort	laps		system protein glial cell in vivo functional evide	numesion more use (Glaat AM) and provide structural and nee for its relevance. A cross-reactive CSF-derived antibody	
omprising more than 10 million young adults on diagnosed with MS during their period of service.	active duty in the US military, 955 of whom were Risk of MS increased 32-fold after infection with EBV but	1		was initially identified b	y single-cell sequencing of the paired-chain 8 cell and CST. followed by protein microarray, based testing of	
vas not increased after infection with other virus	es, including the similarly transmitted cytomegalovirus.	aciem		recombinantly express	ed CSF-derived antibodies against MS-associated viruses.	
BV seroconversion. These findings cannot be ex	arker of neuroaxonal degeneration, increased only arter	02.0		Sequence analysis, affin	ity measurements and the crystal structure of the EBNAI -	
a the leading cause of MS.	Science			the development of		
aultiple scierosis (MS) is a chronic inflammatory de				GlialCAM cross-rea		PAIEM-
nating disease of the central nervous system of unk		City		disease in a mouse		3,2 JEIVI tanta
osogy. The demyesination in the brain and spinal core imune-mediated process (7) possibly triggered by a vir		Science 1		prevalent in patien	BRIEF DEFINITIVE REPORT	
ction (2). Among the putative causal agents, the top e te is Epstein-Barr virus (EBV) (3). EBV is a he	Epstein-Barr virus and multiple	sclerosis		therapies.	Broader Epstein-Barr virus	-specific T cell receptor
rpesvirus that after infection persists in latent form importes throughout the life of the bost (3). A causa					repertoire in patients with	multiple sclerosis
EBV is supported by the increased MS risk after infec	William H. Roomson - and Lawrence Steinman- Deposed immediate and Rearables. Department of Medicine, Starford Diversity, St	unford, CA, USA, FVA Palo Alto Health C	The presence of aligoclonal bands (OCI of therapies that deplete B cells empl	s) in CSF and the efficacy asize the importance of		
BV nuclear antigens (EBNAs) (5), and by the presen	Department of Neurology and Neurological Sciences, Stanford University, Stanford, CA, US	A Email w robinson@stantiand educ stel	8 cells in the pathobiology of M5 ⁷ . And mumps, measles, varicella zoster viru	iviral antibodies against (VZV) and EBV are often	Tilman Schneider Hohendorf" O., Liux Ann Gerden ^{11,44} O., Bilatrice Physilet ¹ Catarina Raposo ⁴ O., Björn Tackenberg ⁴ O., Marianne Repenhausen ¹ O., Cla	**@, Rahvil Gittelman*@, Patrick Ostkang*@, Flarian Rubelt*@, uda jaroschka*@, Christian Warsch*@, Florence BucciareEl*@,
BV in MS demyelinated lesions reported in some (6-8 et all (0), rathelesical studies. Didense of causality	Infection with Epstein-Barr virus is the trigger for the deve	elopment of multiple scle	present in MS ¹⁷ , but their relevance is un-	lear Arti-EBNALantibody	Andrea Flort-Hecht ¹¹⁴ O, Eduardo Debran ¹¹⁴ O, Taria Kangfel ¹¹⁴ O, Kaga David Bourst ¹ O, Kastan J, Walandol ¹¹ O, Martin Kenchentrained ¹¹ O, Luco	Andreger ¹⁴ O, Catharina C, Gross ¹ O, Held Chapmar ¹ O, Lee Kapler ¹ O, Storal O, Lee N, Linearcen ¹ O, Restored Model ¹ O, Bisland J, March
eer, remains inconclusive.	Infection with the Epstein-Barr virus (EBV) has long been pla	semablasts and plasma cells.	the development of clinical symptoms, w	hich providesevidence for	Herr: Wend?"@, and Nichslas Schwab?"@	
Causality implies that some individuals who devel IS after Filly infection would not have developed MS if	postulated to trigger multiple scierosis (MS) (I). Prior anal-	The mechanism (or mecha	an epidemiological link between MS and tious menonucleosis during LBV infect	EBV'. Symptomatic infec- ion increases the risk for	Fastein-Barr view (FRV) infection precedes multiple sclerosis (/	MS) pathology and cross-reactive antibodies might link ERV
ad not been infected with EBV. Ruling out a randor	-99.5% of MS patients compared with +94% of healthy indi-	velopment remains elasive. i micry, through which EBV	developing MS'. Molecular mimicry betw is a potential mechanism that might e	ren vieus and self-antigens velain this association*	infection to CNS autoimmunity. As an altered anti-EBV T cell rea-	ction was suggested in MS, we queried peripheral blood T cell
Ial, the gold standard to study this counterfactual o ence is an "experiment of nature," a longitudinal inve	viduals (2). On page XXX of this issue, Bjornevik et al. (3) has analoged EBV antibodies in series from 801 individuals who	man myelin proteins and ot	Antibodies against certain EBNAI reg	ions have been found in	receptor # chain (TCR#) repertoires of 1,395 MS patients, #87 c multimer-confirmed, viral antieren-specific TCR# sequences. We	ontrols, and 35 monozygotic, MS-discordant twin pairs for detected more NHC I-restricted EBV-specific TCRS
ion of MS incidence in a cohort of EEV-negative individ	developed MS among a cohort of >10 million people active in EE	V transformation of B cells of	(refs. 17-0), which we describe here in our	identification of molecu-	sequences in MS patients. Differences in genetics or upbringing	could be excluded by salidation in monozygotic twin pairs
ome of whom will be infected with EBV during the fo in and some who will not. The ubiquitons nature of	the US military over a 20-year period (1993-2013). Thirty-five sic of the 803 MS cases were initially EBS accompanying and 14	in of pathogenic plasmablas	lar minicry between EBNA1 and GlaIC cance of this minicry in the pathophys	IM. The potential signifi- iology of MS is described	discerdant for MS. Anti-VLA-4 treatment amplified this observa modulate FRV.specific T cell accurrence. In healthy individuals	ition, while interferon B- or anti-CD20 treatment did not ERV.spacific CD3: T cells were of an effecter memory
which infects -95% of adults, and the fact that MS is a	became infected with EBV before the onset of MS. EBV sero-	ane protein 2A (LMP2A) mit	in detail.	00.000000000000000000000000000000000000	phenotype in peripheral blood and cerebrospinal fluid. In MS pat	tients, cerebrospinal fluid also contained EBV-specific central-
ively rare disease, has until now impeded such	positivity was nearly ubiquitous at the time of MS develop- ment with only one of \$22 MS areas being VIV approximation	ling. LMP1 mimics CD	A local alliances appears at the ord of the paper.		memory CDB* T cells, suggesting recent priming. Therefore, MS	is not only preceded by EBV infection, but also associated
irst release: 13 January 2022	at the time of MS onset. These findings provide compelling ter	action. Additionally, EBV e			with product carright in the reportance, constant, with an o	alout morest managements
	data that implicate EBV as the trigger for the development of po	otein, which activates B cell	the secon and its supportation		12(2)(2)(3)	
	How does a virus with tropism for B cells develop into a sh	eath, or defective clearance of	f infected B cells. CD8" T cells		Introduction DV secondersion has been shown in large endemiclorical	subsequent recruitment of peripheral cristenic as well as T
	disease of the central nervous system (CNS)7 In MS, there is an an inflammatory attack against the myelin sheath and the ax-	ecific for EBV lytic proteins a d a nersistent EBV infection	re present in MS brain lesions, a in the CNS might stimulate		studies to precede clinical signs of multiple sclerosis (M3;	helper cells (Bar Or et al., 2021). It has been suggested previously
	ons that it insulates. Ultimately, neurons themselves are in- CI	08' T cell responses that mea	liate CNS injury (4-8) (see the		infection is necessary but not sufficient for disease initiation and	that pergnerat 1 dets show increased cytokine response to ta- tent ESNA-1 epitopes (Lunemann et al., 2006) with presumed
	plasmablasts, express integrin a4, which has adhesive prop-	ure). There are multiple report	is suggesting that molecular		associated central nervous system (CNS) damage. Additionally, antibolis come montivity was detected between a latent stud	cross-reactivity to myelin (Lunemann et al., 2008). However, it has also been discussed that the anti-DRV 2 and conserver in MS
	erties that allow these antibody-producing cells to move from mi	micry might induce MS. Se	rum antibodies from MS pa-		epitope of Epstein-Barr maclear antigen-1 (EBNA-i) and a CNS	patients targets lytic components, indicating orgoing GW ac-
	the bone marrow to the peripheral circulation and then tier	nts to the EBV small capsid p	protein BFRF3 cross-react with		autoantigen (GlaJCAM) in a subset of patients as a hamoral component of and notestial link to., MS perhology (Aluja and	tivity (Angeliei et al., 2013; Lassement et al., 2011) and/ee in- sufficient XBV meeted (Carolina) at al., 2017; Bunder et al., 2010).
	dence inside the brain and its internal lining (4). A distinct my	elination (10). Another stu	dy showed serum antibodies		Salvetti, 2022; Lana et al., 2022). While relaying remitting MS	
	feature of MS is the synthesis of immunoglobulins by clonal fro	m MS patients are cross-real	tive between amino acids 411-		(EEMS) is specifically characterized by the presence of B- and plasma cells in the cerebrospinal fluid (CEF; Gross et al., 2020).	Results and discussion
	munoglobulins, found in cerebrospinal fluid (CSF) from pa-the	human chloride-channel	protein, anoctamin 2 (ANO2),		T cells and macrophages dominate CNS immune cell infibrates in	Quantification of EBV specific, MHC+ restricted TCRB sequences
	tients with MS, are applied to an electrophoretic gel, they wh	ich is associated with elect	rical conduction in axons (11).		influx of T cells (Schneider Hohendorf et al., 2021). This hints at	In light of the finding that EFV infection precedes the develop-
	globulin bands, representing clonal expansions of plas- cru	os-react with myelin basic	protein have also been identi-		recurrent antigen drainage from the CNS into the periphery and	ment of MS and that some MS patients showed cross-reactive
	mablasts. These antibodies target myelin-producing glial fies	t (12). Clonally expanded an	tibodies in the CSF of MS pa-		Tepartment of Neurology with Institute of Translational Neurology, University of Water	ter, Wanter, Germany, "Institute of Clinical Neuroimmunology, University Heightal
	Multiple studies have identified EBV-infected B cells in wit	in the CNS cell adhesion r	nolecule, glialCAM, have also		and Biomedical Center, Sadwig Maximilians Universitit Manches, Munch, Germany, Narthnaved, Germany, "Munich Claster of Systems Reutology DyNergol, Munich, Ge	Bonedical Center, Faculty of Madicine, Luring Maximilians Universite Minchen, many: "Truleuse treations for orfectious and inflammatory diseases (Inferity)
	the brains of MS patients (5, 6). Understanding how infection been been been been been been been be	en described (4). It is intrig	uing that three contiguous re-		University of Toslouus, Centre National de la Recherche Scientifique, Indiant National de Malaptive Bietechnologies, Seattle, WA, Mache Sequencing Solution, Pleasanton, Oc.	e la Semir et de la Recherche Médicale, Université Paul Salarier, Taubison, France, 19. Hulfmann La Roche Ltd, Beist, Switzerland, 1950/pps University, Department
	ot B cetts with EBV initiates the pathology seen in MS is now gio ripe for a deeper understanding of the roles of these clonally EB	ns of mimicry have been re NA-1 protein: this may arise	ported in a small region of the through immune surveillance		of Neurology, Markurg, Garmary, "Pentitute of Legal Medicine, Ludwig Maximiliani 1 Nartinoini, Germany,	Universität Närchen, Marich, Germany, Plentitate for Bological Intelligence,
	expanded B cells and plasmablasts. Depletion of B cells with in	a process called epitope spr	nading.		12. Schooler Haherdorf, LA. Gerdes, II. Pignalet, R. Liblas, H. Wierell, and N. School	th contributed equally to this paper. Comparedence to Nicholas Schwab:
	monocional antibodies targeting CD20 has emerged as one of the most efficacious therapies for MS (7). However, because, orb	Increased incidence of EB	V infection is associated with churing systemic huma envite-		rentette a bealagiskitsen die	
	of the BBB, CD20 monoclonal antibody therapies do not ma	tosus (SLE). Serologic react	ivation of EBV (production of		© 2002 Schnieder Hahendo Fetal, This article is available under a Creative Common: Un Isonners/by/K-00	unos (REPARTOR CE Vienational, as described at https://www.energin.org/
	ies to CD20 do not deplete their progeny, antibody-producing	· service annalogues after re	sommer of acave idlection) is		Rackafeller University Press	https://doi.org/20.3264/jem.20220650 1.of
	Plan advanta 12 Lauran 2022	(Data suphra as	e final of time of first schools) 1		3 Exp. Mud. 2022 Vol. 219 No. 11 420220650	

[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	
How patients with multiple disability Pred D. Lublin, ^{1,1} ©Dieter A. Häring, ^{2,1} @Habib Ganji Brahad Hatami, ³ @Jelena Čuklina, ⁴ @Heit Aarden, ² @ Douglas L. Arnold, ⁴ @Heinz Wiendl, ⁵ Tanuja Chim Bernd C. Kieseier ² and @Robert A. Bermel ²	sclerosis acquire gahi, ³
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 ce independent of relapse activity (PIRA). This study addresses the relative ce delay disability accumulation. Uncertainty of the second study of the second study and patients' multiple sclerosis, we evaluated '202000 Expanded Dinability accumulation, the second study of the second study of the 2020 patients with s15 years follow up. We analyzed here dutasets: (i) vational and randomized controlled dimical traits in which disability accumulation relative importance of RAW and RRA, investigated the relatives in patients' and observed the impact of the mechanism of w on the time to reach nelestone disability levels using the continuous M RRA started 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 (phase 12.4.2.4.2.2.2.2.2.2.2.2.2.2.2.2.2.2.2.2	associated worsening (RAW) or progression nutribution of relapses to disability worsen- tartin to which multiple acterosis theraptice start to which multiple acterosis theraptice start to which multiple acterosis theraptice ling all multiple (EDSS) transitions from A full analysis dataset containing all obser- tions and accuse disability worsening using orsening and disease-modifying theraptes so and accuse disability worsening using orsening and disease-modifying theraptes active models. It has a full active of disability were the principal driver of disability were the principal risk factors for incom- bility (EDSS 1), it took .85 years until in- marky partice of the start of all-cause dis- tersus a year without relapses), the hazard were the principal risk factors for incom- bility (EDSS 1), it took .85 years until in- marky partice of the start of all-cause com- diting therapse therefore EDS starts, these com- d in patients with PIRA and superimposed alily, primarily early in multiple sclerosis, these to cach missione EDS starts and the sclerosis contains driver of disability accumulation cipal risk factors for further disability ac- cural by years, with the potential to gain
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. Advance @ The Authorphy 2022. Published by Oxfard Ubiversity Press on behalf of the Coaranters of Brain. This Is an Cape. Access and the distributed used rule terms of the Oxfard Common Arthronian. New by sul 24(3), which permits more commanded in lessing. Althrough Coaranter Common Arthronian Men were, giving example, forces and permits and example. The Arthronian Men evens, giving example, topical appendixed perpendixed.	nce access publication February 1, 2022 Commercial License (https://cwativecommons.org/licenses/ rouided the original work is properly cited. For commercial



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 (NfL) and glial fibrillary acidic protein (GFAP) planned after approximately half of the 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 1,400 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	30 mg	45 mg	Placebo
and Infestations	IMU-838	IMU-838	
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		۲	•	•	0	•	0	0
Increased Number of Infections	•		•	•	0	•	0	0
Vaccination Limitations	۲	•	•	•	•	0	0	0
Gastrointestinal Toxicities, Incl. Diarrhea	۲	•	0	•	•	•		•
Cardiovascular Risks, Incl. Blood Pressure		0	•		•	•		•
Lymphopenia	۲	0	•	•	•	•	0	0
Neutropenia	۲	•	•	•	•	0	0	0
Risk of Liver Injury	۲	!	0	•	•	•	0	0
Rebound Effect					•	•	•	•
Increased Risk of Cancer	۲		•	•	ļ	0	0	0
Macular Edema	۲	٠	•	•	•	•	•	•
Favorable Profile O Clinical Concern / Risk O 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 1,400 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 feature Current treatment options have serious tolerability downsides

Izumerogant: 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

Izumerogant 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
RORy (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

PBMC: Peripheral Blood Mononuclear Cells; Th: T helper; IL: interleukin; IFN: interferon; MST: microscale thermophoresis [1] Zuoming Sun, City of Hope, 2019

Izumerogant Selectively Inhibits Th17 Differentiation and IL-17 Secretion

The differentiation towards Th17 cells is inhibited by izumerogant

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

The physiological maturation of T cells within the thymus is not affected by izumerogant

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

Izumerogant Does Not Induce Thymocyte Apoptosis

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

Sun, Zuoming. City of Hope, 2021, unpublished

Izumerogant 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 izumerogant **Different gene expression** pattern for apoptosis and proliferation signature genes in **RORγ knockout** and **izumerogant treatment**, but similar for RORγ+/+

Zuoming Sun, City of Hope, 2021

Izumerogant Allows Normal Thymocyte Maturation In Vivo Acute Model, 3 Days of Treatment

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

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

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

Phase 1 Clinical Trial: Trial Design and Current Status

Evaluation of single ascending doses (SAD)

Healthy human subjects randomized to receive single dose of izumerogant or placebo Evaluation of multiple ascending doses (MAD)

Healthy human subjects randomized to receive 14-day treatment of izumerogant or placebo Evaluation of moderate-to-severe psoriasis patients receiving 28-day treatment of izumerogant or placebo

- Dose escalation completed: 100, 200, 300 and 400 mg of izumerogant
- > 79 subjects enrolled
- Izumerogant was well-tolerated and showed dose-linear PK
- Dose escalation completed: 150 mg QD and 150 mg BID of izumerogant
- > 15 subjects enrolled
- Izumerogant was well-tolerated and steadystate was achieved after 3-6 days of dosing
- > 150 mg QD and 150 mg BID of izumerogant
- ➢ 41 patients enrolled
- Detailed evaluation of group-level interim analysis ongoing

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 Izumerogant

F s

Favorable PK Properties for izumerogant at Steady-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

- 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 Izumerogant 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

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

Identifying Therapeutic Activity of Izumerogant 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 izumerogant in patients with moderate-to-severe psoriasis
- Initial two dose cohorts of 150 mg QD and 150 mg BID of izumerogant 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
 - Administration of izumerogant and placebo were safe and well-tolerated, no new safety signals observed
 - Immunic expects to continue izumerogant development in psoriasis and will determine next steps for the program
 - Immunic plans to provide further updates and guidance on potential next steps towards end of Q1/2023

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

Izumerogant 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.
- Izumerogant 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 RORγ 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 Izumerogant in CRPC NCT05124795

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

- Main treatment will be single agent izumerogant 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

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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

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 (OACD) 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

IMU-856 Improves Intestinal Barrier Function

Intestinal permeability was measured as TEER after barrier-disrupting stimulation in Caco-2 cells

48 hours of TNF α challenge followed by 144 hours of IMU-856 treatment

→ IMU-856 was able to restore epithelial barrier integrity after destructive cytokine challenge

TEER: transepithelial electrical resistance; Caco-2 cells: human intestinal epithelial cell line; TNF: tumor necrosis factor; DMSO: dimethyl sulfoxide

Phase 1 Clinical Trial: Trial Design and Current Status

Evaluation of single ascending doses (SAD) Healthy human subjects randomized to receive single dose of 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

Evaluation of multiple ascending doses (MAD)

Healthy human subjects randomized to receive 14-day treatment of IMU-856 or placebo

- 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

Evaluation of patients with celiac disease receiving 28-day treatment of IMU-856 or placebo

- Dosing: 80 and 160 mg QD of IMU-856
- Approximately 42 patients planned to be enrolled
- Currently ongoing
- Initial data expected in mid-2023

QD: quaque die = once-daily

Dose-Linear Pharmacokinetics in Multiple Dosing Part B, Multiple Ascending Doses, Day 1 and 14

Mean plasma concentrations over time by treatment Part B (linear)

- 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 dose-proportional increase in plasma C_{max} and AUC
- Accumulation factor of ~1.5 allowing predictable trough levels and drug exposure after once-daily oral administration

	Day 1			Day 14, steady state			
Value (mean)	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: 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 Patients with Celiac Disease During Periods of GFD and Gluten Challenge

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 assessments include chronic disease markers (Vh:CrD) and patient reported outcomes
- Performed at sites in Australia and New Zealand

Day 1-28: Treatment IMU-856/placebo Day 14-28: Gluten challenge with 6 g/daily Day 29: Baseline: Day 14: EGD with EGD with IL-2 biopsy biopsy Lactulose/Mannitol test: Baseline, Day 8, Day 14, Day 29 Celiac disease symptom diary and impact of celiac disease symptoms questionnaire

Flow Chart of Part C in Celiac Disease

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

Interleukin-2 Correlates With Onset and Severity of Symptoms

Serum Interleukin-2 elevations correlate with onset and severity of symptoms after gluten exposure in patients with celiac disease^[1]

Elevated as early as 2 hours post gluten challenge (peak level at 4 hours)^[2]

Figure Ref [1]

[1] Tye-Din et al., Aliment Pharmacol Ther. 2019;50:901–910 [2] Goel et al., 2019 British Society for Immunology, Clinical and Experimental Immunology, 199: 68–78

IMU-856 Could Present a New and Innovative Approach for the Treatment of Gastrointestinal Diseases

- 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 investigational medicinal product-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.

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 izumerogant: 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 mid-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 116.4 million (as of Dec 31, 2022) Shares outstanding: 44,403,838 (as of Feb 17, 2023)

Summary: Several Clinical Data Readouts Expected in 2023

Initial phase 1b celiac disease data expected in mid-2023

Interim analysis of phase 2 CALLIPER trial in progressive multiple sclerosis estimated for H2/2023

Update and guidance on potential next steps for phase 1 trial in psoriasis towards end of Q1/2023

Thank You!

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