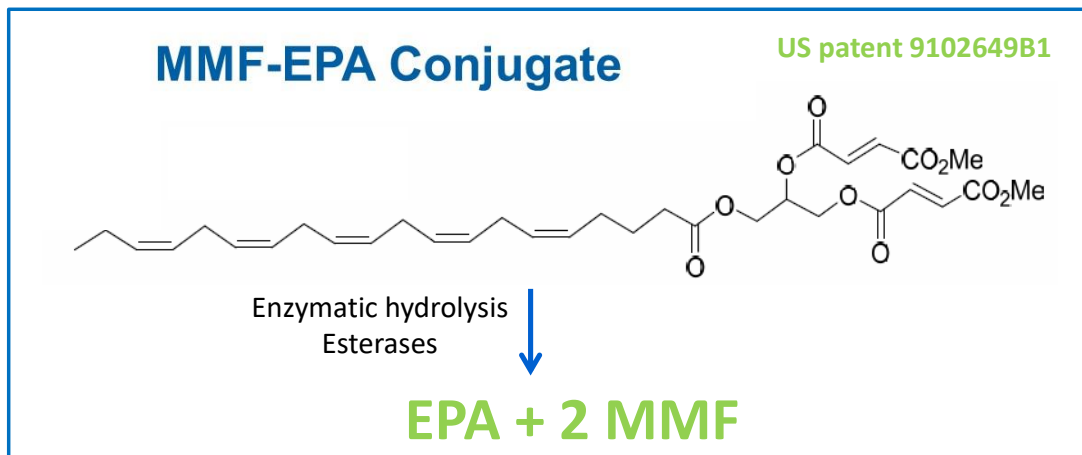


# VCB-101

NOVEL MOLECULAR CONJUGATES OF  
MONOMETHYL FUMARATE  
FOR THE TREATMENT OF  
MULTIPLE SCLEROSIS AND PSORIASIS



### Executive Summary

- ✚ VCB-101 and other monomethyl fumarate (MMF) conjugates and co-salts have good physicochemical characteristics
- ✚ VCB-101 shows more sustained levels of MMF in preclinical studies
- ✚ Oral dosing of VCB-101 results in elevated plasma levels of both MMF and EPA
- ✚ VCB-101 is expected to exhibit enhanced efficacy due to longer duration of action as compared to Tecfidera
- ✚ VCB-101 expected to reduce flushing and gastrointestinal events
- ✚ Strong Intellectual Property – Patent portfolio

### Opportunity Overview

VClinBio (VCB) utilizes expertise in monomethyl fumarate (MMF) chemistry and biology to discover and develop innovative drug products for treatment of immune diseases and other related diseases. Each of the novel VClinBio candidates is based on an approved drug or previously studied, biologically active agent. We use our VCB Technology to provide better pharmacokinetic, pharmacodynamic or physicochemical properties to enable development of known agents for existing, new, previously unattainable indications. VCB Technology also offers an approach to drug discovery and clinical development that is more efficient and less expensive than conventional small molecule drug research and development. VClinBio is implementing this approach to develop a robust pipeline of new medicines addressing unmet medical needs. The novel MMF conjugates (VCB-101 and VCB-102) upon hydrolysis release MMF, the same active drug of Tecfidera (dimethylfumarate).

Tecfidera, a prodrug of MMF, is approved for the treatment of multiple sclerosis. Besides MMF, our novel MMF conjugates also release eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA), components that are shown to possess added beneficial effects.

Our drug product candidates have strong intellectual property protection including composition of matter, treatment, process, formulation and physical combination claims.

## PIPELINE

Pipeline Code	Description	Design	Chemistry	Pre-Clinical	Delivery Mode	Regulatory Strategy
VCB 101	A Novel Glycerol Molecular Conjugate of MMF and EPA	→			Oral, I.V.	505(b)(2) US
VCB 102	A Novel Glycerol Molecular Conjugate of MMF and DHA	→			Oral, I.V.	505(b)(2) US
VCB 103	Ionic Salt: MMF -Piperazine-EPA	→			Topical, I.V.	505(b)(1)
VCB 104	Ionic Salt: MMF-Piperazine-DHA	→			Topical, I.V.	505(b)(1)
VCB 105	A Novel Prodrug of MMF: HCl salt	→			Oral	505(b)(2)
VCB 106	Ionic Salt: MMF-EDA-EPA	→			Topical, I.V.	505(b)(1)
VCB 107	Ionic Salt: MMF-EDA-DHA	→			Oral	505(b)(1)

## About Multiple Sclerosis

Multiple sclerosis (MS) is a chronic and progressive inflammatory neurodegenerative disease in which body's immune system attacks myelin proteins that insulates neuronal axons. The disease typically strikes in young adulthood and because it is progressive in nature, disability accumulates over time and can lead to permanent impairment of mobility, cognition and the ability for self-care.

According to the National Multiple Sclerosis Foundation, there are estimated to be 400,000 people with MS in the United States. More than two-thirds of MS patients are women and relapsing forms of the disease accounts for approximately 65% of MS patients. Most people are diagnosed between the ages of 20 and 50, although MS can occur in young children and significantly older adults.

Patients often exhibit an initial clinically isolated syndrome, followed by a series of subacute clinical events that spontaneously abate, referred to as relapsing remitting MS (RRMS). While patients generally return to near normal neurologic function at the cessation of each episode, over a variable period of time there can be irreversible progression of clinical disability termed secondary progressive MS (SPMS), although early therapeutic intervention may delay time to progression. However, 10%–15% of MS patients will instead experience primary progressive MS (PPMS), characterized by clinical progression from the initiation of disease without preceding relapses and remissions. About 5% of the patients show progressive disease with clear relapse exacerbations of the disease characterized as progressive relapsing multiple sclerosis (PRMS).

## Scientific Rationale – Multiple Sclerosis

### Fumarate esters exert anti-inflammatory and neuroprotective effects

Inflammation plays a central role in multiple sclerosis (MS) and glial cells are the effector cells of neuroinflammation by releasing various kinds of pro-inflammatory cytokines (i.e. TNF- $\alpha$ , IL-1 $\beta$ , IL-6) or pro-inflammatory molecules like nitric oxide (NO). In the pathological course of multiple sclerosis (MS) autoreactive lymphocytes gain access to the central nervous system, initiating a cascade of events leading to demyelination, axonal transection, and neurodegeneration occurs at an early stage. Oxidative stress associated with reactive oxygen and nitrogen species is implicated as a significant factor in the pathology of MS. Extensive neuronal loss and gliosis are evident in the later stage of the disease process.

Growing evidence supports that, while an inflammatory pathology characterizes the early relapsing stage of multiple sclerosis, neurodegenerative pathology dominates the later progressive stage of the disease. Multiple sclerosis disease-modifying therapies currently in development attempt to specifically target the underlying pathology at each stage of the disease, while avoiding frequent self-injection. Therefore the initiation of treatment for multiple sclerosis early in the disease will reduce the potential for increase in damage and could be a clinically meaningful approach. Dimethyl Fumarate (DMF) is a drug approved to treat patients with relapsing forms of multiple sclerosis has shown to provide the anti-inflammatory and neuroprotective mechanism of action. DMF is indicated for relapsing forms include relapsing-remitting MS, progressive-relapsing MS, and secondary-progressive MS in those people who continue to have relapses.

### Omega-3 fatty acids exhibit anti-inflammatory and immunomodulatory effect in multiple sclerosis

Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are the two main forms of n-3 PUFAs in the brain. Several epidemiological studies suggest that n-3 PUFA supplementation is associated with improved clinical outcomes (reduction in relapse rate and favorable effect in disease activity) in MS patients. Beneficial effects of n-3 PUFA supplementation have also been reported in the experimental autoimmune encephalomyelitis (EAE) animal model of MS and attributed to the modulatory effect of docosahexaenoic acid (DHA) on dendritic cell-dependent T cell activation.

## Unmet Medical Need – Multiple Sclerosis

Tecfidera currently approved immunomodulatory therapies for multiple sclerosis (MS) show modest efficacy (30 to 68%) or can produce a wide range of adverse effects ranging from GI upset and flushing (DMF). The actions of DMF are mediated by MMF. Although the treatment options for the management of relapsing–remitting multiple sclerosis (RRMS) are increasing rapidly, these therapies need to improve the patient compliance, by reducing the efficacious dose thereby reducing the side-effects.

Flushing and gastrointestinal (GI) adverse effects (e.g., nausea, vomiting, abdominal pain and diarrhea) were reported more frequently in delayed-release tecfidera–treated patients. Data from the phase 3 clinical studies has showed that GI adverse effects were reported by 42% of patients receiving delayed-release DMF and 4% discontinued study treatment owing to these events. Similarly, flushing was reported in 36% of patients receiving delayed-release DMF and study treatment discontinuation owing to flushing was reported in 2% of patients. Flushing response is characterized by severe reddening of the skin, itching, and tingling. Several studies have shown that flushing occurs in response to the vasodilatory effects of prostaglandin D2 (PGD2) and prostaglandin E2 (PGE2), and their metabolites. A variety of symptomatic treatments were utilized during the delayed-release DMF clinical trials in patients presenting with delayed-release DMF–related flushing or GI adverse effects that were severe or bothersome enough to warrant pharmacological intervention. Anti-inflammatory drugs like (Aspirin 325 mg) is one of the most commonly used drugs before each delayed-release DMF dose. The incidence of flushing and GI tolerability events was highest in the first month and decreased substantially in subsequent months.

Novel MMF conjugates and salts with more favorable pharmacokinetic and efficacy profile will provide more effective therapy with reduced adverse effects.

VCB-101 or VCB-102 is expected for:

- ✚ First line of therapy for multiple sclerosis
  - **Superior / equal** to Tecfidera in efficacy
  - Improved **safety** over Tecfidera due to EPA/DHA co-availability
  - Potential benefit in **anti-inflammatory property** and disease modification due to synergistic pharmacology on monomethyl fumarate with EPA or DHA
  
- ✚ **Oral** route of administration

## About Psoriasis

Psoriasis is the most common autoimmune disease in the United States. It is a relapsing and remitting immune-mediated inflammatory disease that affects the skin and joints. Plaque psoriasis, a chronic inflammatory skin disease, accounts for 80-90% of all psoriasis patients and appears as raised, red patches covered with a silvery white buildup of dead skin cells, typically found at the elbows, knees, scalp and genital area. Psoriasis is associated with comorbid conditions, including depression, arthritis, diabetes, hypertension, metabolic syndrome and cardiovascular events, and has a major impact on health-related quality of life, affecting daily activities of 60% of patients with moderate-to-severe psoriasis.

It is estimated that psoriasis affects 2% of the population worldwide, including approximately 6 million people in the United States, and that 20-30% of psoriasis patients have moderate-to-severe psoriasis.

Although psoriasis can affect all age groups, the onset of psoriasis tends to peak between the ages of 20 and 30 and between ages 50 and 60.

## Scientific Rationale - Psoriasis

### Fumaric acid esters in psoriasis

Fumaric acid ester (FAE) therapy has proved effective in patients with severe psoriasis vulgaris. FAE therapy is licensed in Germany and registration is pending in many European countries. Multicenter trials have confirmed the beneficial effect of FAE in psoriasis. Nonclinical experiments revealed that FAEs mediate anti-inflammatory, immune-modulatory and anti-proliferative effects.

### Omega-3 fatty acids as an anti-inflammatory and immunomodulatory drug in Psoriasis

Supplementary treatment with omega-3 polyunsaturated fatty acids (PUFAs) complements topical treatment in psoriasis, and makes a significant contribution to reducing Psoriasis Area and Severity Index (PASI); and in reducing scalp lesion and pruritus, erythema, scaling, and infiltration of the treated areas. Several studies have been performed to evaluate the efficacy of the daily supplementation of EPA and DHA in patients with psoriasis, with an improvement observed in their mean PASI score, as well as in clinical symptoms, particularly in pruritus.

DHA and EPA (PUFAs) roles in the skin includes maintenance of the stratum corneum permeability barrier, maturation and differentiation of the stratum corneum, formation and secretion of lamellar bodies, inhibition of pro-inflammatory eicosanoids, elevation of the sunburn threshold, inhibition of pro-inflammatory cytokines (tumor necrosis factor-alpha, interferon-gamma, and interleukin-12), inhibition of lipoxygenase and promotion of wound

healing. PUFAs play a key role as immune response modulators and suppressors of immunologic functions.

### Unmet need - Psoriasis

There are systemic and topical therapies for the treatment of psoriasis. Fumaric acid esters (FAE) have been used to treat psoriasis in Northern Europe, but yet to approved for Psoriasis treatment in the United States. Common adverse events associated with FAE therapy for psoriasis are gastrointestinal complaints and flushing. Gastrointestinal adverse events, such as diarrhea, mild stomach upsets, stomach cramps, fullness and flatulence, occur in more than two-thirds of patients and are most frequently reported between 4 and 12 weeks of treatment. Approximately one-third of patients experience flushing, characterized by reddening of the face and a sensation of heat, sometimes associated with headache, lasting minutes to hours. Flushing occurs most often at the onset of treatment and becomes less frequent with further exposure. Gastrointestinal adverse events and flushing together lead to discontinuation of FAE therapy in approximately 7% of patients. Overall, the rate of discontinuation due to adverse events and/or noncompliance with treatment is 30-40%. The inconvenience of taking up to three daily doses, and the requirement for frequent laboratory monitoring, may also represent significant barriers to treatment. VCB-101 series is expected to offer significant improvement in the therapeutic outcome over the current available oral medications.

### Preclinical Summary

Salient characteristics observed in preclinical studies of VCB-101 are indicated below. Biopharmaceutical properties including Log P, Log  $D_{pH7.4}$ , solubility, stability in biological matrices are suitable for developing the for oral dosing. VCB-101 is highly stable in Simulated Gastric Fluid (SGF), but undergo rapid hydrolysis in Simulated Intestinal Fluid (SIF) and liver microsomal studies. These characteristics of VCD-101 makes it a suitable prodrug for the delivery of MMF to the small intestine.

Pharmacokinetics studies after oral dosing indicate that MMF-EPA conjugate (36.3 mg/kg) when compared with DMF (16.7 mg/kg) at comparable doses produced reduced  $C_{max}$ , increased half-life, and reduced total levels of MMF. When the pharmacokinetics studies were carried out after oral dosing of MMF-EPA conjugate (217 mg/kg) in comparison with DMF (100 mg/kg), the MMF-EPA conjugate produced reduced  $C_{max}$ , and increased half-life with no change in total levels of MMF. MMF-EPA conjugate also elevated plasma levels of EPA that remained elevated more than 24hr post MMF-EPA conjugate dosing. Our studies indicate that the MMF-EPA conjugate has a differentiated MMF pharmacokinetic profile that may translate to reduced dosing frequency and reduced side effect as compared to DMF. Co-release of EPA from MMF-EPA indicate potential additive/synergistic anti-inflammatory effects, and increase efficacy of the MMF-EPA conjugate.

### Plasma concentration of MMF or EPA in rats following single oral dose of DMF or MMF-EPA conjugate

Compound	Dose mg/kg	Plasma Analyte	C <sub>max</sub> (ng/ml)	AUC ng*hr/ml	Half-life (hr)
Dimethyl Fumarate	16.7	MMF	4985 ± 116	1574 ± 62	0.1 ± 0.01
MMF-EPA Conjugate	36.3	MMF	825 ± 116*	1030 ± 107*	0.5 ± 0.16*
Dimethyl Fumarate	100	MMF	12783 ± 2571	10868 ± 531	1.2 ± 0.23
MMF-EPA Conjugate	217	MMF	3835 ± 397*	9851 ± 867	3.7 ± 1.56*
MMF-EPA Conjugate	217	EPA	31137 ± 4586	377018 ± 53968	6.0 ± 2.32

Dimethyl fumarate (16.7 mg/kg) is equivalent to MMF-EPA conjugate (36.3 mg/kg). Dimethyl fumarate (100 mg/kg) is equivalent to MMF-EPA conjugate (217 mg/kg). Data presented are mean ± SD (n=4). C<sub>max</sub>: maximum observed plasma concentration; AUC: the area under the plasma concentration-time curve from 0 to last measurable time point; Half-life: the time required for the concentration of the compound to reach half of its original value. Asterisks represents significant difference as compared to DMF, unpaired two-tailed Student's t test.

### Chemistry Manufacturing Controls

The major attributes of VCB-101 conjugates and salts are:

- ✚ Uncomplicated and Optimized Synthesis
- ✚ Economical and availability of key intermediates and chemicals
- ✚ A conventional or delayed release oral dosage form for the treatment of multiple sclerosis and psoriasis or topical formulation for the treatment of psoriasis could be easily developed

### Intellectual Property

Our drug product candidates have strong intellectual property protection including composition of matter, treatment, process, formulation and physical combination claims, US 9102649 B1 and US 9580383 B2.

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