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Review Article

Topical gene editing therapeutics using lipid nanoparticles: 'gene creams' for genetic skin diseases?

Ina Guri-Lamce,[1] Yara AlRokh,[1] Youngah Kim,[1] Ruhina Maeshima,[2] Carina Graham,[2] Stephen L. Hart,[2] John A. McGrath[1] and Joanna Jacków-Malinowska[1]

[1]St John's Institute of Dermatology, King's College London, London, UK
[2]Genetics and Genomic Medicine Department, UCL Great Ormond Street Institute of Child Health, UCL, London, UK
Correspondence: Joanna Jacków-Malinowska. Email: joanna.jackow@kcl.ac.uk

Abstract

Patients living with inherited skin diseases have benefited from recent advances in DNA sequencing technologies that provide new or improved diagnostics. However, developing and delivering new treatments for the 'genodermatoses' remains challenging. The goal of creating topical preparations that can recover the inherent gene pathology remains largely aspirational. However, recent progress in two fields – the chemistry of topical delivery formulations (lipid nanoparticles) and the molecular biology of gene repair (CRISPR-Cas9, base and prime editing) – presents new opportunities to address this unmet need. In this review, we discuss how lipid nanoparticle delivery vehicles could be used to deliver gene-editing tools to formulate topical 'gene creams' suitable for the treatment of genodermatoses. We summarize the historical landscape of topical therapeutics and advances in gene editing that may herald an era of new therapies for patients with inherited skin disorders.

Introduction

In skin disease, topical treatments are an attractive alternative to systemic therapies and have a high potential for clinical translation. The skin is a readily accessible organ, making the assessment of disease progress and treatment monitoring easier. In addition, the biomolecules comprising topical treatments are not subject to catabolism in the bloodstream or liver, improving bioavailability at their site of action. Lipid nanoparticles (LNPs) are promising, clinically relevant delivery platforms that have been shown to enhance the delivery of therapeutic biomolecules to the skin. Importantly, LNPs are capable of packaging and delivering gene editing tools, offering a precise means of therapeutically manipulating the human genome. Therefore, it is clear that the delivery of gene editing tools using LNPs has significant potential to treat genodermatoses. This review describes the progress and challenges of overcoming the skin barrier for topical delivery to the skin, explains the currently available approaches to gene editing and describes how LNPs are promising tools for the delivery of gene editing therapies. Finally, it lays out the perspectives and considerations of topical gene editing therapeutics using LNPs.

Delivery of treatments via the skin: a historical perspective

Drugs have been applied topically to the skin for thousands of years to treat skin conditions and manage systemic ailments.[1] Therapeutic use of topical delivery systems has increased markedly since the late twentieth century, when the first transdermal drug delivery patch (Transderm Scop®) gained US Food and Drugs Administration (FDA) approval in 1979, delivering scopolamine to treat motion sickness,[2] and the first topical liposome formulation (Pevaryl®), delivering the antifungal drug econazole, was introduced in 1994.[3] The percutaneous absorption of various steroids, such as cortisone, oestradiol and testosterone, was reported in 1969,[4] and – to this day – steroids remain a key class of topically delivered drugs (e.g. topical glucocorticoids for the treatment of several inflammatory dermatoses).[5] Steroids are a unique class of topical active pharmaceutical ingredients (APIs), as they require a balance in their delivery between reaching sufficient concentrations in the epidermis while avoiding such deep penetration that they cause systemic toxicity. Around this time, it was discovered that the formulation of the delivery vehicle plays a large role in determining the penetration of an API into the skin. The size, surface charge, lipophilicity and deformability will determine the mechanism and depth of deposition into the skin.[6–8] Lipid-based delivery systems, particularly newer-generation LNPs, may disrupt and infiltrate the lipids of the stratum corneum (SC) and enhance absorption into deeper layers of the skin.[6,9–11] Scientific progress has led to numerous APIs being delivered topically, using various delivery systems. Notably, the first *in vivo* topical gene therapy for any genodermatoses (Vyjuvek™; Krystal Biotech, Pittsburgh, PA, USA) gained FDA approval in 2023 for the treatment of dystrophic epidermolysis bullosa (DEB) wounds. Vyjuvek delivers two copies of the normal *COL7A1* coding sequence to skin cells through an engineered, nonreplicating *COL7A1*-containing herpes simplex virus type 1 (HSV-1).[12,13] HSV-1 has a payload capacity of around 150 kb,[14] and can efficiently infect cells and resist immune clearance. In the clinical trials, Vyjuvek was mixed with an excipient gel before being

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applied topically to wounds, resulting in the closure of most treated wounds within 3 months of treatment, as opposed to wounds treated with a placebo, which inconsistently healed and re-blistered over time. This was the first trial to show that the topical application of gene therapy for skin diseases is possible and its success suggests that other gene therapy systems (e.g. gene editors) could be delivered to the skin using LNPs to achieve longer-lasting treatment with less frequent administration.

Is the skin barrier a challenge or an open door for topical treatment? How can we reach the target cells?

The barrier function of the skin prevents the entry of harmful substances or pathogens from our environment. However, this makes topical delivery particularly challenging. The sites of action for most skin-specific APIs are at the viable cells of the epidermis and dermis. These lie below the stratum corneum (SC), which constitutes the primary skin barrier and is comprised of layers of keratin-filled corneocytes that are embedded in a continuous, highly lipophilic lipid matrix.[15] Several routes can facilitate penetration of the SC. Firstly, APIs can pass through the SC via the transepidermal and transappendageal pathways (Figure 1a).[16] The transepidermal pathway can be further divided into intracellular or intercellular pathways and is limited to small lipophilic molecules.[17–19] With regard to the intracellular route, APIs pass through aqueous pores of approximately 40 nm diameter in the corneocytes.[20–22] The intercellular pathway is the major transepidermal entry route and involves APIs diffusing through the continuous lipid matrix of the SC, although this is limited to very small molecules with a diameter < 10 nm.[16] In the transappendageal pathway, the hair follicles and sweat glands in the skin result in a 'shunt' pathway that permits hydrophilic and higher-molecular-weight compounds (< 600 nm) to pass through and access deeper layers of the skin.[8,10,23] Secondly, in the bulge of hair follicles reside follicular stem cells, which are bipotent not only in that they differentiate into hair follicle cells, but also epidermal keratinocytes in response to wounding.[24,25] Follicular stem cells are therefore a repository of keratinocyte stem cells and so targeting and editing this population may mean a longer-lasting or even permanent one-off treatment.

The skin barrier in many genodermatoses is altered through pathogenic variants in genes encoding components of epidermal cells, the extracellular lipid matrix or cell–cell/cell–extracellular matrix interactions.[26–28] This may increase permeability enough to allow for the delivery of larger molecules,[18,29] such as gene editors, without the need for external disruption methods.

Why is gene editing a promising permanent treatment for inherited skin diseases?

Gene editing repairs disease-causing variants by precisely exchanging the incorrect sequences in DNA or by providing compensatory healthy copies of endogenously mutant genes. There are different systems available to use, depending on the target and cell type. The most well-known gene editing system is CRISPR-Cas9.[30] It relies on creating a double-stranded break (DSB) in the DNA, followed by one of two endogenous DNA repair mechanisms: nonhomologous end joining (NHEJ) or homology-directed repair (HDR) (Figure 1b). NHEJ is the most common DSB repair mechanism, although it is error prone and results in undesired genetic insertions and deletions. Conversely, the preferable HDR mechanism requires an exogenous DNA template to encode the repair, resulting in precise gene editing with infrequent errors. However, HDR relies on pathways only active in dividing cells, making it unusable in terminally differentiated cells; additionally – even in dividing cells – NHEJ pathways dominate.[31]

CRISPR-Cas9 has been used to edit induced pluripotent stem cells (iPSCs) derived from patients with recessive DEB (RDEB) via electroporation,[32] to edit – using viral vectors – patient-derived keratinocytes for junctional epidermolysis bullosa,[33] and to target *COL7A1* in RDEB keratinocytes using a commercial nanoparticle-based system.[34] CRISPR-Cas9 has also been used in a HeLa cell line established to be heterozygous for a pathogenic mutation in *Krt9* to model epidermolytic palmoplantar keratoderma using viral vectors.[35] Although CRISPR-Cas9 has advanced the field of gene editing, the risks associated with DSBs make it unfavourable for *in vivo* therapeutic application. Newer gene editing strategies – which function without creating DSBs, such as cytosine base editors (CBEs),[36,37] adenine base editors (ABEs)[38,39] or prime editors[40] – have been created to overcome this limitation. The repair mechanism of base editors relies on deaminase activity, while prime editing relies on reverse transcriptase.[41] Base editors have been used to edit RDEB patient-derived fibroblasts and iPSCs, and have shown higher correction efficiencies than previously reported CRISPR-Cas9 pathways.[42,43] Prime editing has been used to produce modifications of RDEB patient-derived fibroblasts of up to 10.5%.[44]

All the aforementioned types of gene editors can be delivered in three different functional formats: (i) DNA (typically in plasmid form); (ii) mRNA; and (iii) directly in protein form as a ribonucleoprotein (RNP) complex (Figure 1d). The RNP consists of a nuclease-based protein and a guide RNA (gRNA) that directs the complex to the location of editing; structures of gRNAs, nucleases and accessory proteins depend on which editing technology is used. In gene editing, the RNP can be thought of as the API.[45] The pathway leading to the RNP complex formation in the cell depends on the format of the gene editing agent delivered. The former two modes rely on postdelivery intracellular expression and complexing of RNP components, while the latter involves direct delivery of preformulated RNP to the cell.[46] Historically, DNA has been the most common format, but mRNA is fast becoming the more popular method owing to its greater safety, control of expression and ease of manufacture.[47,48]

However, gene editors in all formats are rapidly degraded *in vivo*, and cell membranes are impermeable to them, necessitating their encapsulation in a delivery vehicle to access target cells and perform their function.[49,50] Delivery systems can be broadly broken down into physical, viral or nonviral. LNPs – the focus of this review – constitute a nonviral approach in which gene editing components in all formats (DNA, mRNA or RNP) can be encapsulated and delivered,[51] although the delivery of RNA, in particular, has

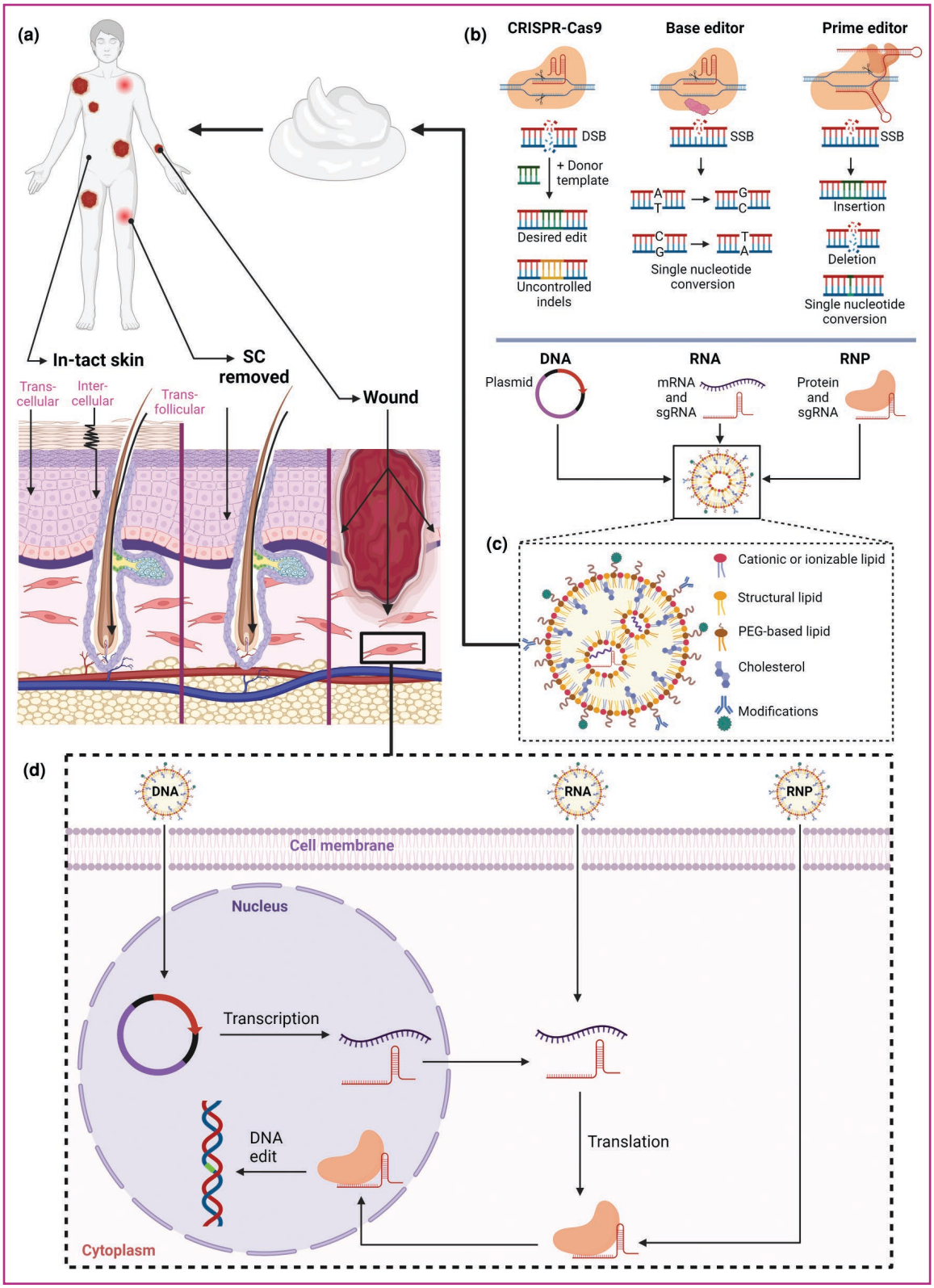

Figure 1 Topical gene editing therapeutics using lipid nanoparticles. (a) Schematic showing the structure of healthy/intact skin vs. skin with a compromised stratum corneum (SC) and vs. wounded skin. Distinct delivery routes of therapeutics to the skin are also shown. (b) A summary of the types of gene editors (CRISPR-Cas9, base editors, prime editors) and their formats of delivery (DNA, mRNA, ribonucleoprotein [RNP]). (c) Composition of a standard lipid nanoparticle (LNP) for delivery of a therapeutic. The cargo depicted here is mRNA and single guide RNA (sgRNA), although LNPs can equally package RNP and DNA, and can be delivered topically to patients using an excipient gel or cream as in (a). (d) Mechanism of action of different formats of gene editors once inside the cell, here a fibroblast. DSB, double-stranded break; PEG, polyethylene glycol; SSB, single-stranded break.

gained traction recently.[52,53] The distinct delivery systems have been thoroughly reviewed elsewhere, including the detailed chemistry of LNPs and their components, and we refer the reader to these reviews for further information.[50,52,54–57]

Lipid nanoparticles are a platform technology: can they deliver gene editing agents?

What are lipid nanoparticles?

LNPs are synthetic, spherical vesicles that usually have four components: (i) a cationic or ionizable lipid; (ii) a structural lipid otherwise referred to as a helper lipid or phospholipid; (iii) a polyethylene glycol (PEG)-based lipid; and (iv) cholesterol (Figure 1c).[52,57,58] A huge advantage of LNPs is that they are flexible in their design and can be formulated with some or all these components. The modularity of LNPs means that there is scope to add additional components, including anionic lipids, cell-targeting peptides, polysaccharides and minerals.[59–64] Combinatorial chemistry can be employed to develop many unique lipid compositions in a single process,[65–68] and strategies such as selective organ targeting have been developed that enable controllable delivery to target tissues,[69] meaning that libraries of many chemically distinct lipid delivery systems are being developed that have potential to be applied to many clinical *in vivo* gene editing approaches (Table 1).

How have lipid nanoparticles been used to deliver gene editing therapies so far?

While LNPs have been widely approved for the delivery of small molecules, including chemotherapy drugs,[70] small interfering RNA (siRNA)[71,72] and mRNA,[52,73] research into LNPs for gene editing purposes is primarily in the preclinical stages. *In vivo* work has begun to increase, and several clinical trials are now underway.

In vitro *delivery*

Cationic LNPs have been used to deliver CRISPR-Cas9/single guide (sgRNA) RNPs and base editors in plasmids/RNPs into several mammalian cell types.[37,74] Second-generation ionizable LNPs have also been used to deliver gene editing therapies *in vitro*. For example, they have been used to deliver CRISPR-Cas9/sgRNA RNPs to green fluorescent protein (GFP)-expressing human embryonic kidney cells, with gene editing-mediated loss of up to 70% of GFP expression,[67] and to deliver the prime editor PE3 mRNA/sgRNA/pegRNA to a HAP1 reporter cell line, resulting in editing rates of 54%.[75]

In vivo *delivery: systemic*

When delivered systematically, LNPs tend to aggregate and are cleared by the liver, meaning that most *in vivo* gene editing work to date has focused on the liver as a target tissue.[2,50,76] Ionizable lipids have been used to deliver CRISPR-Cas9 mRNA/sgRNA intravenously in mouse models to knock down *pcsk9* with up to 90% efficiency;[77] to mediate *angptl3* knockdown in the mouse liver that remained stable 100 days after a single dose;[78] and to knock down by $>95\%$ serum transthyretin levels for at least 12 months.[79] The latter formulation is now being tested in a phase I clinical trial of intravenous injection to target the liver to treat amyloid transthyretin amyloidosis (ClinicalTrials.gov: NCT04601051).[80] This trial is a major milestone, marking the first use of *in vivo* gene editing in humans. Ionizable LNPs have also been used to deliver base editors systemically, for example to deliver CBE mRNA/sgRNA to the mouse liver to target the faulty *Pah* gene, enabling correction of disease phenotype without detectable off-target deamination on the transcriptome and genome.[81] This system was then used to deliver an ABE8 base editor variant intravenously to knockdown *PCSK9* in the liver of cynomolgus monkeys, with a reduction of PCSK9 (proprotein convertase subtilisin/kexin type 9) of approximately 90% observed, remaining stable for at least 8 months after a single-dose treatment.[82] This has now moved on to a phase I clinical trial to deliver ABE8 mRNA and sgRNA to target *PCSK9* and treat heterozygous familial hypercholesterolaemia (ClinicalTrials.gov: NCT05398029).

Owing to the innate liver tropism after systemic delivery, LNPs must be modified for systemic *in vivo* gene editing in other tissues.[69] Groups have now started to develop specific organ-targeting LNPs. For example, a lung-targeting LNP was used to deliver CRISPR-Cas9 mRNA and LoxP-targeting sgRNA intravenously into Ai14 mice.[83] Moreover, another group delivered CRISPR-Cas9 RNP and sgRNA intravenously in a mouse model, systematically adjusting the molar percentages of components in the LNP. They found that increasing cationic lipid content caused tropism to the lung rather than liver and they were also able to demonstrate successful simultaneous editing of multiple genes in the lungs.[74] This exciting work shows that gene editing can be targeted to specific tissues simply by adjusting the LNP component chemistry and ratios.

In vivo *delivery: local*

Local delivery of gene editing therapy using LNPs to specific target tissues is often more desirable because this strategy avoids metabolism in the bloodstream or liver and reduces the risk of off-target editing in non-target tissue. In one study, LNPs containing Cre recombinase protein were successfully delivered into the tdTomato-expressing mouse brain by local injection for Cre-mediated gene recombination. As a proxy for gene editing as described in this review, this demonstrates the potential potency of LNPs for RNP complex delivery to nonliver tissues *in vivo*.[67,68] Similar LNPs have also successfully edited *in vivo* with CRISPR-Cas9 mRNA and sgRNA when injected locally into the brain and muscle of tdTomato-expressing (Ai9) mice.[74] The same LNPs were used to deliver CRISPR-Cas9 mRNA and sgRNA into tibialis anterior muscles of humanized Duchenne muscular dystrophy (DMD) mice, with around 4.2% of dystrophin protein restoration observed as a result of mutation correction. Another study also reported LNP delivery of CRISPR-Cas9 mRNA and sgRNA into skeletal muscle of humanized DMD mice by repeated intramuscular injections into a humanized mouse model, inducing stable genomic exon skipping and restoring dystrophin protein. The low immunogenicity of the LNP also allowed for repeated administration of the treatment, with a dose-dependent increase in dystrophin observed.[84] LNPs have also been used to deliver CRISPR-Cas9 mRNA/sgRNA

Table 1 A summary of lipid nanoparticles (LNPs) used for preclinical gene editing applications

Components in the LNP										
Cationic or ionizable lipid	**Structural lipid**	**PEG-lipid**	**Cholesterol**	**Gene editor type**	**Gene editor format**	**Approximate LNP size (nm)**	**Target gene**	**Target cell/ tissue**	**Delivery method**	**Study**
X-O14B	DOPE	C16-PEG2000 ceramide	Cholesterol	CRISPR-Cas9	RNP and sgRNA	290	*GFP*	GFP reporter HEK cells	*In vitro*	Wang *et al.*[67]
MC3	DSPC	PEG2000-DMG	B-sitosterol	Prime editor (PE3)	mRNA, sgRNA and pegRNA	80	emGFP-linker–TGA-mCherry	HAP1 reporter cells	*In vitro*	Herrera-Barrera *et al.*[75]
LP01	DSPC	PEG2000-DMG	Cholesterol	CRISPR-Cas9	mRNA and sgRNA	105	*Ttr*	Mouse liver	Systemic – IV injection	Finn *et al.*[79]
BAMEA-O16B	DOPE	PEG2000-DSPE	Cholesterol	CRISPR-Cas9	mRNA and sgRNA	230	*Pcsk9*	Mouse liver	Systemic – IV injection	Liu *et al.*[77]
FTT5	DOPE	PEG2000-DMG	Cholesterol	ABE	mRNA and sgRNA	100	*Pcsk9*	Mouse liver	Systemic – IV injection	Zhang *et al.*[100]
306-O12B	DOPC	PEG2000-DMG	Cholesterol	CRISPR-Cas9	mRNA and sgRNA	110	*Angptl3*	Mouse liver	Systemic – IV injection	Qiu *et al.*[78]
Undisclosed ionizable lipid	DSPC	Undisclosed PEG lipid	Cholesterol	CBE (CBE3)	mRNA and sgRNA	70	*Pah*	Mouse liver	Systemic – IV injection	Villiger *et al.*[81]
Undisclosed ionizable lipid	DOPC	Undisclosed PEG lipid	Cholesterol	ABE (ABE8.8)	mRNA and sgRNA	100	*PCSK9*	Monkey liver	Systemic – IV injection	Musunuru *et al.*[82]
5A2-DOT-5	DOPE	PEG2000-DMG	Cholesterol	CRISPR-Cas9	RNP/sgRNA	100–200	*P53*, *Pten*, *Rb1*, *Pcsk9*	Mouse liver	Systemic – IV injection	Wei *et al.*[74]
5A2-DOT-50	DOPE	PEG2000-DMG	Cholesterol	CRISPR-Cas9	RNP/sgRNA	100–200	*tdTomato P53*, *Pten*, *Eml4*, *AlkRb1*	Mouse lung	Systemic – IV injection	Wei *et al.*[74]
306-N16B	DOPC	PEG2000-DMG	Cholesterol	CRISPR-Cas9	mRNA and sgRNA	80	LoxP	Mouse lung	Systemic – IV injection	Qiu *et al.*[83]
8-O14B	DOPE	C16-PEG2000-ceramide	Cholesterol	(–27) GFP–Cre	RNP/sgRNA	100–240	*tdTomato*	Mouse brain	Local injection	Wang *et al.*[67]
Lipid 8	DSPC	DMG-PEG DSPE-PEG	Cholesterol	CRISPR-Cas9	mRNA and sgRNA	80	Plk1	Mouse hippocampal tumour	Local injection	Rosenblum *et al.*[85]
5A2-DOT-10	DOPE	PEG2000-DMG	Cholesterol	CRISPR-Cas9	RNP/sgRNA	100–200	tdTomato	Mouse muscle and brain	Local injection	Wei *et al.*[74]
5A2-DOT-10	DOPE	PEG2000-DMG	Cholesterol	CRISPR-Cas9	RNP/sgRNA	100–200	*Dmd*	Mouse muscle	Local injection	Wei *et al.*[74]
TCL053	DPPC	PEG2000-DMG	Cholesterol	CRISPR-Cas9	mRNA and sgRNA	80	*Dmd*	Mouse muscle	Local injection	Kenjo *et al.*[84]
RCB-4-8	DOTAP	C14-PEG2000	Cholesterol	CRISPR-Cas9	mRNA and sgRNA	85	*tdTomato*	Mouse lung	Local – intratracheal administration	Li *et al.*[65]

ABE, adenine base editor; CBE, cytosine base editor; DMG, dimyristoylglycerol; DOPC, 1,2-dioleoyl-sn-glycero-3-phosphocholine; DOPE, dioleoylphosphatidylethanolamine; DOTAP, 1,2-dioleoyl-3-trimethylammonium-propane; DPPC, dipalmitoylphosphatidylcholine; DSPC, 1,2-distearoyl-sn-glycero-3-phosphocholine; DSPE, 1,2-dioctadecanoyl-sn–glycero-3-phosphoethanolamine; emGFP, emerald green fluorescent protein; GFP, green fluorescent protein; HAP1, near-haploid human cells derived from KBM-7 cell line; HEK, human embryonic kidney; IV, intravenous; PEG, polyethylene glycol; pegRNA, prime editing guide RNA; RNP, ribonucleoprotein; sgRNA, single guide RNA; TGA-mCherry, mCherry preceded by the stop codon TGA, such that editing of the stop codon allows for mCherry fluorescence.

into induced hippocampal tumours in mice to target *Plk1*. This resulted in 68% gene editing *in vivo*, which caused tumour cell apoptosis and inhibited tumour growth by 50%, increasing survival rates.[85] Finally, LNPs have been used to deliver CRISPR-Cas9 mRNA/sgRNA intratracheally to Ai9 mice, achieving 7.5% expression of tdTomato.[65] These LNPs are now being explored for nebulization, to make formulations more clinically relevant for lung diseases.

Are lipid nanoparticles appropriate delivery vehicles for skin-specific gene therapies?

A summary of LNPs used for *in vivo* gene therapy into the skin is provided in Table 2. Interestingly, there have been no reports of gene editing in skin *in vivo*, although skin has been a target for nucleic acid-based gene therapies using LNPs. Lipofectamine™ 2000 (ThermoFisher Scientific, Waltham, MA, USA) has been used to deliver elastin mRNA into *ex vivo* porcine skin via intradermal injection, increasing *de novo* elastin production in the skin by 20%; [86] however, Lipofectamine cannot be used *in vivo*, owing to its cytotoxicity.[67] A proprietary ionizable lipid has recently been used in an LNP formulation to deliver vascular endothelial growth factor A (VEGF-A) mRNA via intradermal injection into a C57BL/6 diabetic mouse model. LNP/VEGF-A mRNA-treated wounds had an average area of 2.4% vs. 21.4% in the control group. Histological analysis confirmed the healing efficacy and showed low toxicity of the formulation, indicating that these LNPs can successfully deliver mRNA into cells and significantly accelerate diabetic wound healing.[87] LNPs have also successfully delivered siRNA topically to normal and psoriatic human *ex vivo* skin biopsies.[20,88] Adding sodium cholate and ethanol increased the deformability of the LNPs, allowing them to cross the intact human epidermal membrane and deliver siRNA into keratinocytes of the viable epidermis.[89] In another study, LNPs containing sodium cholate were confined to the SC in normal skin but could penetrate the different layers of the epidermis in psoriatic skin due to the impaired barrier.[88] LNPs could penetrate all the epidermal layers in normal and psoriatic skin; in the latter, they were used to deliver *DEFB4* siRNA to downregulate beta-defensin 2 mRNA expression to 70% compared with untreated controls, with a significant decrease in protein expression.[88] Most recently, CRISPR-Cas9 mRNA or RNP-loaded LNPs were delivered *in situ* into a three-dimensional skin model, achieving editing rates of 5–12% when coupled with pretreatment of the skin.[90] While this editing efficiency is lower than that achieved *in vitro* by the same LNPs into primary human keratinocytes (up to 72%), to our knowledge, this is the first report of *in situ* gene editing in the skin.

What considerations need to be made for topical gene editing therapeutics using lipid nanoparticles?

Firstly, the LNPs must overcome the skin barrier, otherwise the treatment will be ineffective or demand excessive dosages for therapeutic effect. A main consideration is the size of the LNP; sufficiently small LNPs are required to penetrate deeper layers of skin, so they can enter the relevant cells via endocytosis and deliver the gene editors into their

Table 2 A summary of lipid nanoparticles (LNPs) used for *in vivo* gene therapy into the skin

Components in LNP						Approx. LNP size (nm)	Target gene	Tissue target	Delivery method	Study
Cationic or ionizable lipid	**Structural lipid**	**PEG-lipid**	**Cholesterol**	**Other**	**Cargo**					
MC3	DOPE	Undisclosed PEG-lipid	Cholesterol	ApoE	CRISPR-Cas9 mRNA and sgRNA	25-36	*HPRT*	3D human skin model	Topical application with microneedle or fractional ablative laser	Bolsoni *et al.*[90]
Lipid H (proprietary)	DOPE	Undisclosed PEG-lipid	Cholesterol	ApoE	CRISPR-Cas9 RNP and sgRNA	200–280	*HPRT*	3D human skin model		
DOTAP	None	None	Cholesterol	Sodium cholate and ethanol	Cy5-siRNA	60	NA	*Ex vivo* human skin	Topical application	Geusens *et al.*[89]
DOTAP	None	None	Cholesterol	Sodium cholate	Cy5-siRNA	150	NA	*Ex vivo* human skin	Topical application	Desmet *et al.*[88]
DOTAP	DOPE	None	Cholesterol	None	Cy5-siRNA	170	NA	*Ex vivo* human skin		
DOTAP	DOPE	None	Cholesterol	None	DEFB4 siRNA	150	*DEFB4*	*Ex vivo* psoriatic human skin		
L546-1	DSPC	PEG2000-DMG	Cholesterol	None	VEGF-A mRNA	100	None	C57BL/6 diabetic mouse skin	Intradermal injection	Zha *et al.*[87]
DOSPA(LF2000)	NA	NA	NA	None	Elastin mRNA	NA	None	*Ex vivo* porcine skin	Intradermal injection	Lescan *et al.*[86]

3D, three-dimensional; ApoE, apolipoprotein E; DEFB4, defensin beta 4; DMG, dimyristoylglycerol; DOPE, dioleoylphosphatidylethanolamine; DOSPA, 2,3-dioleyloxy-N-[2-(sperminecarboxamido)ethyl]-N,N-dimethyl-1-propanaminium; DOTAP, 1,2-dioleoyl-3-trimethylammonium-propane; DSPC, 1,2-distearoyl-sn-glycero-3-phosphocholine; NA, not applicable; PEG, polyethylene glycol; sgRNA, single guide RNA; siRNA, small interfering RNA; VEGF-A, vascular endothelial growth factor A.

cytoplasm. LNPs can be modulated to adjust their size, and most novel LNPs developed for gene editing purposes are around 100 nm in diameter (Table 1). Several studies have shown that LNPs with a diameter of $\leq$ 100 nm can penetrate and allow onset of action of the API into deeper layers of skin.[7,10,11] Therefore, based on their size, LNPs currently used for gene editing in other tissues should also be suitable for topical delivery in the skin. The components selected in the LNP formulation is another design consideration and influences size, among other things. Cationic and ionizable LNPs have both been used in skin applications, in preclinical *in vivo* animal studies and *ex vivo* human skin grafts (Table 2), as well as in many gene editing applications in other tissues (Table 1).[86–89] There are studies to suggest that LNPs containing positively charged lipids trigger the infiltration of leucocytes, the secretion of large amounts inflammatory cytokines and inflammatory pathway activation in mice.[91] More comparative and human-relevant skin-specific studies are necessary to determine the inflammatory effects and determine which lipid type is superior, although by extrapolating data from general gene editing research, it appears that either are likely to work well for topical therapies. With a local treatment, where the LNP is applied directly into the target tissue to be edited, long-term circulation time and systemic shielding is not so relevant, meaning protective PEG-based lipids may be less relevant.[58,64] This is important because there is growing evidence that PEG administration in humans induces anti-PEG antibodies, which leads to a reduction in the therapeutic efficacy of drugs containing PEGs, particularly when re-dosing.[92] As LNPs can be functionalized very easily, one can envisage an LNP system incorporating skin cell-targeting and penetrating functional moieties to enhance tropism to skin cells. For example, a novel peptide sequence was discovered through phage display that enhanced delivery through intact skin.[93] Incorporating such peptides into LNPs provides additional functionality by enabling the LNP to overcome cellular barriers and escape endosomes more effectively.[60–62] Co-delivery with other small molecules may also be possible for a combined effect and a more potent therapeutic.[94]

Secondly, beyond just the LNP formulation, the method of application to the skin must be considered when developing a topical LNP-based treatment. LNPs are prepared as watery, fluid dispersions and would therefore need to be incorporated into an excipient gel or cream so that they stay in place at the delivery site. The chemistry of this biomaterial and interactions with the LNP must be considered, ensuring that it does not cause dissolution or aggregation of the LNPs.[95]

Lastly, the regulatory hurdles of *in vivo* gene editing must be considered and are yet to be fully established. Gene editing therapies are personalized medicine, with a unique sgRNA required to aim for each specific variant to be targeted. It remains unclear how such a therapy will be regulated, for example whether each unique combination of sgRNA and gene editor will need its own approvals. Nonetheless, many genodermatoses will fall under the orphan disease category, which may fast track regulatory processing and speed up clinical translation.[51,96] Several clinical trials are ongoing for gene editing therapy and – considering how new the technology is – the transition from 'bench to bedside' has thus far been remarkable.[97] As well as elucidating the safety of the gene editor itself, conclusive mechanistic studies to demonstrate the delivery efficacy of LNPs are essential, as differences in conditions make it difficult to correlate between LNP activity *in vitro* and *in vivo*. In dermatology, this is compounded by the lack of suitable disease models. Most data from gene therapy and gene editing studies are generated from animal models, particularly mouse models. Mouse models are useful for studying the systemic response, but mouse skin differs drastically from human skin to the point where the relevance of mouse models is heavily questioned.[51,98] What is clear is the need for human-relevant models so that the findings can be translated. This holds especially true for gene editing, where the correction is so specific that animal models and even *ex vivo* human skin grafts may not harbour the correct variants. Patient-derived tissue-engineered human skin equivalents (HSEs) are useful because they can model disease morphology, validate gene editing outcomes and demonstrate expression, secretion, processing and assembly of proteins post-treatment.[32,42,99] However, HSEs are difficult to generate, have a limited lifespan and cannot yet capture the complexity of skin to a relevant enough level that would increase the translational value of early preclinical phases. Ultimately, no perfect model to study the LNP delivery of gene editors exists and this is an area that needs more attention.

Conclusions and future prospects

LNPs are a technology that can deliver a variety of cargos.[57,73] The library of available LNP components is ever increasing, which will facilitate the customized design of treatments for a wide variety of disease targets.[74] Taking the findings from studies of LNP-delivered gene therapy for the skin and LNP-delivered gene editors to other tissues (Tables 1, 2), it is reasonable to assume that LNPs can also be used to deliver gene editors to the skin because: (i) the components used in the formulations are similar; (ii) the size of the cargos is similar; and (iii) the size of the LNPs is similar. Although currently unreported, we expect to see studies emerging in the not-too-distant future.

Overall, for a topical gene editing therapy for genodermatoses to become a reality, the editor itself must be safe without inducing unwanted off-target effects elsewhere in the genome; the correction efficacy must be sufficient to restore function; and the delivery vehicle must be able to bypass the skin barrier to target the appropriate cells. The new generation of gene editors, in combination with LNPs, is showing promise in satisfying these requirements and shaping up to be the new frontier in the treatment of all genetic diseases, although clinically appropriate models are required to validate this in skin. Clinical translation of topical gene editing therapy will be transformative on the burden of genodermatoses and, potentially, other skin diseases.

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Conflicts of interest

The authors declare no conflicts of interest.

Data availability

No new data were generated.

Ethics statement

Not applicable.

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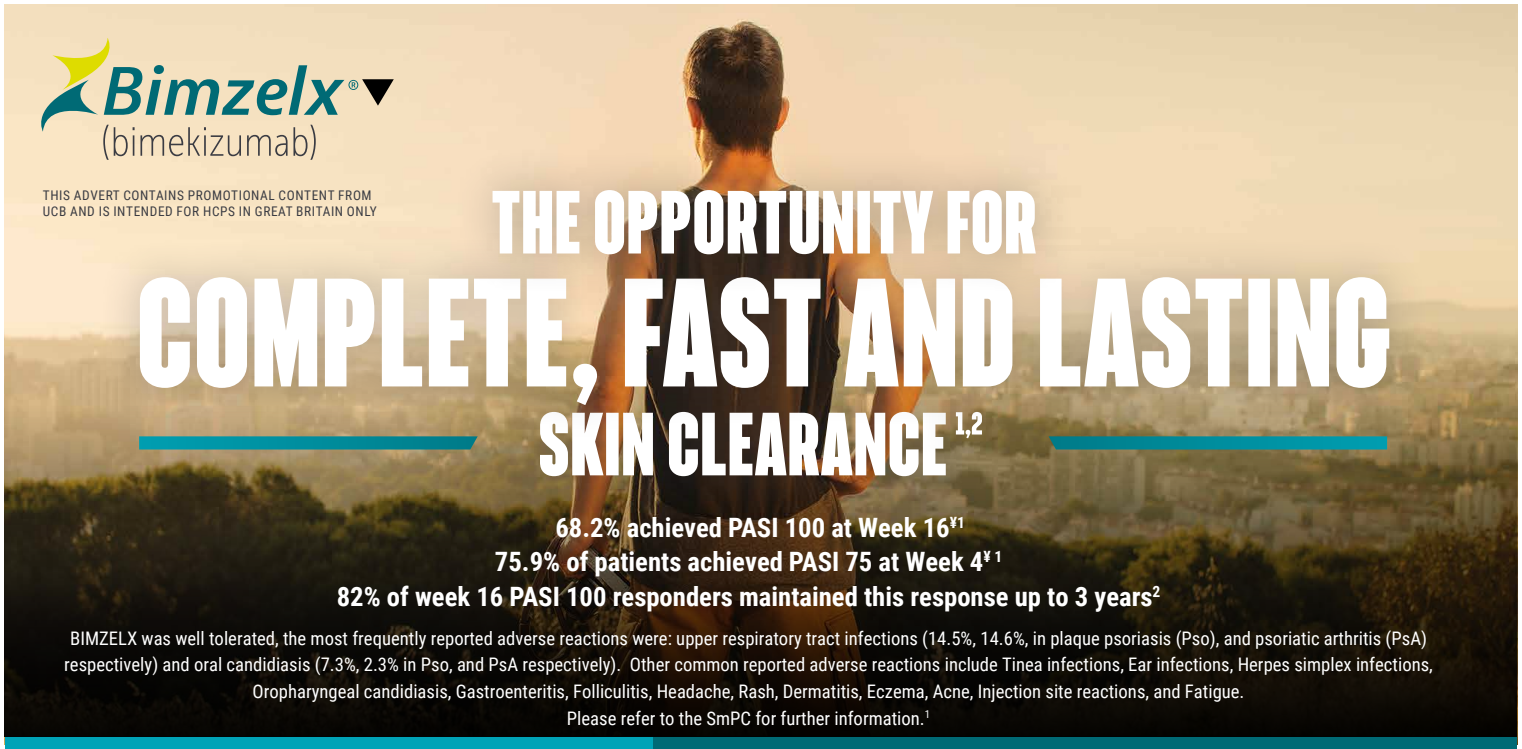

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BIMZELX® (Bimekizumab) is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. Bimzelx, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs). Please refer to the SmPC for further information.[1]

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BIMZELX® ▼ (Bimekizumab) is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy; and for active psoriasis arthritis in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs), alone or in combination with methotrexate.[1] (Please consult the Summary of Product Characteristics (SmPC) before prescribing).

Active Ingredient: Bimekizumab – solution for injection in pre-filled syringe or pre-filled pen: *160 mg of bimekizumab in 1 mL of solution (160mg/mL).* **Indications:** Moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. Alone or in combination with methotrexate, for active psoriatic arthritis in adults who have had an inadequate response or intolerant to one or more disease-modifying antirheumatic drugs (DMARDs). Adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have responded inadequately or are intolerant to non-steroidal anti-inflammatory drugs (NSAIDs). Adults with active ankylosing spondylitis who have responded inadequately or are intolerant to conventional therapy. **Dosage and Administration:** Should be initiated and supervised by a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated. **Recommended dose:** Plaque Psoriasis: 320 mg (given as two subcutaneous injections of 160 mg each) at week 0, 4, 8, 12, 16 and every 8 weeks thereafter. Psoriatic arthritis: 160 mg (given as 1 subcutaneous injection of 160 mg) every 4 weeks. For psoriatic arthritis patients with coexistent moderate to severe plaque psoriasis, the recommended dose is the same as for plaque psoriasis. After 16 weeks, regular assessment of efficacy is recommended and if a sufficient clinical response in joints cannot be maintained, a switch to 160 mg every 4 weeks can be considered. Axial spondyloarthritis (nr-axSpA and AS): 160 mg (given as 1 subcutaneous injection) every 4 weeks. For patients with plaque psoriasis (including psoriatic arthritis with coexistent moderate to severe psoriasis) and a body weight ≥ 120 kg who did not achieve complete skin clearance at week 16, 320 mg every 4 weeks after week 16 may further improve treatment response. Consider discontinuing if no improvement by 16 weeks of treatment. Renal or hepatic impairment: No dose adjustment needed. Elderly: No dose adjustment needed. Administer by subcutaneous injection to thigh, abdomen or upper arm. Rotate injection sites and do not inject into psoriatic plaques or skin that is tender, bruised, erythematous or indurated. Do not shake pre-filled syringe or pre-filled pen. Patients may be trained to self-inject. **Contraindications:** Hypersensitivity to bimekizumab or any excipient; Clinically important active infections (e.g. active tuberculosis). **Warnings and Precautions:** Record name and batch number of administered product. *Infection:* Bimekizumab may increase the risk of infections e.g. upper respiratory tract infections, oral candidiasis. Caution when considering use in patients with a chronic infection or a history of recurrent infection. Must not be initiated if any clinically important active infection until infection resolves or is adequately treated. Advise patients to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops an infection, the patient should be carefully monitored. If the infection becomes serious or is not responding to standard therapy do not administer bimekizumab until infection resolves. *TB:* Evaluate for TB infection prior to initiating bimekizumab – do not give if active TB. While on bimekizumab, monitor for signs and symptoms of active TB. Consider anti-TB therapy prior to bimekizumab initiation if past history of latent or active TB in whom adequate treatment course cannot be confirmed. *Inflammatory bowel disease:* Bimekizumab is not recommended in patients with inflammatory bowel disease. Cases of new or exacerbations of inflammatory bowel disease have been reported. If inflammatory bowel disease signs/symptoms develop or patient experiences exacerbation of pre-existing inflammatory bowel disease, discontinue bimekizumab and initiate medical management. *Hypersensitivity:* Serious hypersensitivity reactions including anaphylactic reactions have been observed with IL-17 inhibitors. If a serious hypersensitivity reaction occurs, discontinue immediately and treat. *Vaccinations:* Complete all age appropriate immunisations prior to bimekizumab initiation. Do not give live vaccines to bimekizumab patients. Patients may receive inactivated or non-live vaccinations. **Interactions:** A clinically relevant effect on CYP450 substrates with a narrow therapeutic index in which the dose is individually adjusted e.g. warfarin, cannot be excluded. Therapeutic monitoring should be considered. **Fertility, pregnancy and lactation:** Women of child-bearing potential should use an effective method of contraception during treatment and for at least 17 weeks after treatment. Avoid use of bimekizumab during pregnancy. It is unknown whether bimekizumab is excreted in human milk, hence a risk to the newborn/infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Bimzelx therapy. No data available on human fertility. **Driving and use of machines:** No or negligible influence on ability to drive and use machines. **Adverse Effects:** Refer to SmPC for full information. Very Common *(≥ 1/10):* upper respiratory tract infection; Common *(≥ 1/100 to < 1/10):* oral candidiasis, tinea infections, ear infections, herpes simplex infections, oropharyngeal candidiasis, gastroenteritis, folliculitis; headache, rash, dermatitis and eczema, acne, injection site reactions, fatigue; Uncommon *(≥ 1/1,000 to < 1/100):* mucosal and cutaneous candidiasis (including oesophageal candidiasis), conjunctivitis, neutropenia, inflammatory bowel disease. Storage precautions: Store in a refrigerator (2°C – 8°C), do not freeze. Keep in outer carton to protect from light. Bimzelx can be kept at up to 25°C for a single period of maximum 25 days with protection from light. Product should be discarded after this period or by the expiry date, whichever occurs first.

Legal Category: POM

Marketing Authorisation Numbers: PLGB 00039/0802 (Pre-filled Syringe), PLGB 00039/0803 (Pre-filled Pen).

UK NHS Costs: £2,443 per pack of 2 pre-filled syringes or pens of 160 mg each.

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Further information is available from: UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire, SL1 3WE. Tel: 0800 2793177 Email: ucbcares.uk@ucb.com

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Bimzelx is a registered trademark.

Adverse events should be reported. Reporting forms and information can be found at http://www.mhra.gov.uk/yellowcard. Adverse events should also be reported to UCB Pharma Ltd at ucbcares.uk@ucb.com or 0800 2793177.

References: 1. BIMZELX (bimekizumab) SmPC. Available at: https://www.medicines.org.uk/emc/product/12834/smpc. Accessed September 2023 **2.** Strober et al. [BE BRIGHT open label extension] Br J Dermatol. 2023. 188(6): 749-759.

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Inspired by patients. Driven by science.

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