SHL MEDICAL

SHL MOLLY® AUTOINJECTORS: POWERING THE NEXT WAVE OF CARDIOMETABOLIC CARE

In this article, Lars Berger, Senior Manager, and Eric Linvill, PhD, Senior CAE Engineer, both at SHL Medical, discuss the rapid growth of the cardiometabolic disease space in light of the global obesity epidemic and how advanced autoinjector and injection pen technologies, such as SHL's Molly platform, will be necessary to meet the challenges presented by this disease area.

The rapid growth of glucagon-like peptide-1 receptor agonists (GLP-1RA) for the treatment of obesity has drawn public attention to treatments for cardiometabolic diseases. With an already significant demand for such treatments that is expected to grow further, the interest in new drug development in this area is increasing. Most of these medications require injectable formats, creating a need for user-friendly autoinjector devices that are readily available to the pharmaceutical industry on a large and unprecedented scale.

ADDRESSING THE BURDEN OF OBESITY AND OTHER METABOLIC DISEASES

The pervasiveness of obesity continues to be staggering. According to the latest available data published in The Lancet, more than a billion people worldwide are living with obesity. In the US alone, the 2022 adult prevalence rate for obesity ranged from 37.7–47.7%. Global estimates for the year 2035 show that no apparent reversal of the trend is coming, with 1.9 billion people expected to be affected. Now recognised as an epidemic – referred to as "globesity" by the WHO – there is increasing pressure on hospitals and clinics, as the centre of care, to treat obesity and other related diseases medically.[1–4]

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In addressing this global epidemic, it is important to acknowledge the relationship between obesity and other cardiometabolic diseases. For this, one is reminded of the strong link between obesity and metabolic syndrome (MetS). In the words of the American Heart Association and the National Heart, Lung, and Blood Institute, MetS is a "constellation of interrelated risk factors of metabolic origin". Such cardiometabolic risk factors, the most widely recognised of which include dyslipidaemia, hypertension and elevated plasma glucose, have been shown to promote the development of atherosclerotic cardiovascular disease (ASCVD). At the same time, MetS has been reported to increase the risk of Type 2 diabetes (T2D).[5–8]

The clear links between MetS, its underlying risk factors and resultant diseases such as ASCVD and T2D open many pathways to treating such cardiometabolic conditions clinically, together or individually. As such, it becomes increasingly clear that treatment delivery must go beyond the contemporary focus on obesity and recognise the network of interrelated cardiometabolic diseases that lie in front.

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GLP1-RA	Date of First Approval	Elimination Half-Life	Administration Schedule	Pharmaceutical Company
SUBCUTANEOUS INJECTIONS				
Short-acting compounds				
Exenatide b.i.d	2005 (US); 2006 (Europe)	3.3–4.0 hrs	Twice daily	AstraZeneca
Lixisenatide	2013 (Europe); 2016 (US)	2.6 hrs	Once daily	Sanofi
Long-acting compounds				
Liraglutide	2009 (Europe); 2010 (US)	12.6–14.3 hrs	Once daily	Novo Nordisk
Exenatide once weekly	2012	3.3–4.0 hrs	Once weekly	AstraZeneca
Dulaglutide	2014	4.7–5.5 days	Once weekly	Eli Lilly and Company
Albiglutide	2014 (Europe & US)	5.7–6.8 days	Once weekly	GlaxoSmithKline
Semaglutide	2017 (US); 2019 (Europe)	5.7–6.7 days	Once weekly	Novo Nordisk
Fixed-dose combinations				
Liraglutide & Insulin degludec	2014 (Europe); 2016 (US)	12.6–14.3 hrs	Once daily	Novo Nordisk
Lixisenatide & Insulin glargine	2016 (US); 2017 (Europe)	2.6 hrs	Once daily	Sanofi
ORAL ADMINISTRATION				
Long-acting compound				
Semaglutide	2020	5.7–6.7 days	Once daily	Novo Nordisk

Table 1: A non-exhaustive list of GLP1-RAs that have been approved to treat T2D. Elimination half-lives were adapted from a 2021 review paper by Nauck *et al.* The list does not include compounds that are still in development or where available information is scarce, such as efpeglenatide, beinaglutide and PEG-loxenatide. Exenatide was also launched as a once-weekly autoinjector in 2018, marketed as BYDUREON® BCise™ (AstraZeneca).[9,10,11]

As preventative care has shown little success in halting the rise in cardiometabolic diseases, new medicines will be crucial for improving the quality of life and independence of as many patients as possible. As research and development in GLP1-RAs and other cardiometabolic treatments continues to evolve, so too does the opportunity to enable at-home patient care with pen injectors and autoinjectors. At-home drug delivery opens pathways to unburden primary care services and enables treatment strategies in safe and easy-to-use self-injection formats. For pharma and biotech companies with cardiometabolic compounds in the pipeline, selecting the right device partner is critical to ensuring a successful launch and continued success.

A HIGH FUTURE GROWTH FOR INCRETIN MIMETICS AND AT-HOME DRUG DELIVERY

Progress in the science of GLP1-RAs has come a long way (Table 1). Since the isolation of glucose-dependent insulinotropic polypeptide (GIP) in the 1970s, further progress has been made in incretin biology, leading to the discovery of the physiological actions of GLP-1 receptor agonists. However, it was only in 2012 – roughly a decade ago – that once-weekly GLP-1RAs were launched. This started with the launch of the long-acting/extended release exenatide microspheres, followed by dulaglutide and albiglutide in 2014.[10] Interestingly, perhaps the most successful of this wave of once-weekly products, dulaglutide, was launched in a three-step autoinjector, which compared favourably with formulations that required more complicated preparation steps for the user.

Not long after, the therapeutic impact of GLP1-RAs expanded from diabetes to chronic weight management for adults with obesity. Key compounds that come to mind are semaglutide, marketed as Wegovy® by Novo Nordisk, and Eli Lilly's tirzepatide, marketed as Zepbound®. The further enhanced effects of these second-generation compounds on lowering blood glucose, reducing weight, and protecting the heart and kidneys, is now encouraging further clinical development and points to many possible novel combinations of medicines in the future.

TREATMENT OF CARDIOMETABOLIC DISEASES ASKS FOR SPECIFICALLY DESIGNED DELIVERY DEVICES

Today, there are more than two dozen therapeutic candidates in the GLP-1 drug class undergoing clinical research. Depending on the API and the formulation, these drugs require a variety of delivery devices, ranging from multi-dose pen injectors to syringe- and cartridge-based autoinjectors. Additionally, these treatments are being developed for conditions such as obesity, diabetes and metabolic dysfunction-associated steatohepatitis (MASH), where patients may potentially require the simultaneous use of multiple medications. Each medication, in turn, requires a specific delivery device technology.[12]

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"Since 2015, SHL has supported the launch of six combination products indicated for cardiometabolic diseases, including incretin mimetics for T2D and obesity in particular, as well as PCSK9 inhibitors for hyperlipidaemia."

Reflecting on the success of already-marketed devices, it is evident that future cardiometabolic treatments will rely in large part on proven drug delivery technologies, like two-step single-use autoinjectors. Whether for novel compounds or generics, such molecules will require user-friendly self-injection solutions developed by a device partner with proven expertise in producing devices for this emerging disease area.

A DECADE OF EXPERIENCE IN CARDIOMETABOLIC DISEASES

With more than 30 years of industry experience in total – resulting in more than 50 combination products – the last ten years has seen SHL tackling a plethora of device projects in collaboration with pharma companies, particularly in the cardiometabolic disease area. Since 2015, SHL has supported the launch of six combination products indicated for cardiometabolic diseases, including incretin mimetics for T2D and obesity in particular, as well as PCSK9 inhibitors for hyperlipidaemia.

In so doing, SHL delivered at least 49.5 million devices into the hands of patients living with cardiometabolic diseases in 2023 alone, a number unrivaled in the field of proprietary autoinjector technology. Further analysis of IQVIA data suggests that SHL's devices have supported the treatment journey of at least 1.6 million patients in this therapeutic area (Figure 1).

Many of these combination product launches relied on SHL's modular Molly platform autoinjectors (Figure 2). In drug-device projects within the cardiometabolic area, the demand is often high. Pharma and biotech companies need partners with proven device technologies supported by a globally dispersed infrastructure capable of scaling manufacturing. They also need to ensure high satisfaction rates for end users. SHL's Molly autoinjector has consistently met this challenge – the modular platform has been integral to the second-generation GLP1-RAs approved for T2D (in Japan in 2020) and obesity (in the US in 2021).[13,14]

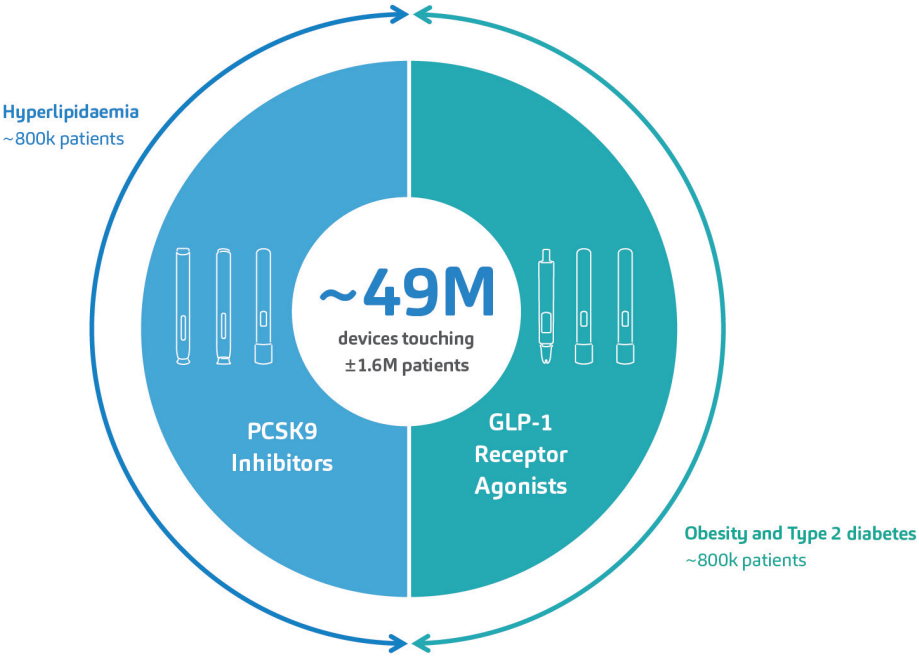

Figure 1: SHL's devices have supported the launch of six combination products for the treatment of cardiometabolic diseases within the last 10 years. An analysis of market data by IQVIA indicates that SHL's devices have touched at least 1.6 million patients afflicted with hyperlipidaemia, T2D or obesity. These numbers do not include emergency combination product treatments for severe hypoglycaemia.

Figure 2: Built upon proven experience in the cardiometabolic space, SHL's modular Molly platform autoinjectors are well positioned to address the up-and-coming developments in this therapy area.

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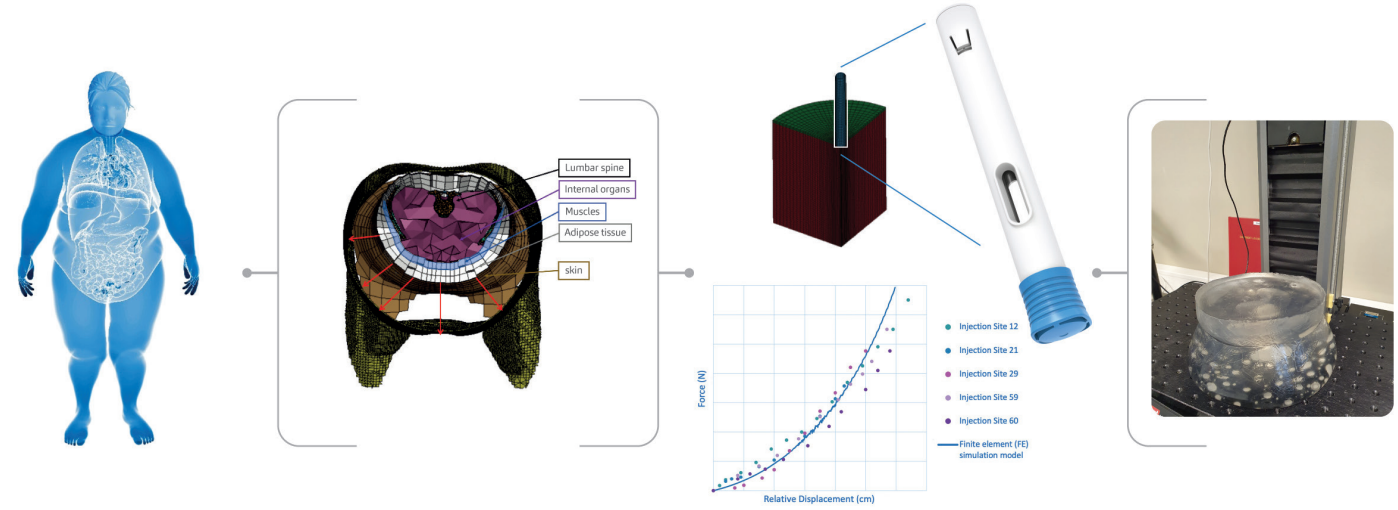

Figure 3: As part of SHL's efforts to advance the understanding of autoinjector activation even in the softest injection sites, SHL's research team presented the proceedings of a study at the 2023 Parenteral Drug Association (PDA) Universe of Pre-Filled Syringes and Injection Devices Conference.[20]

The Molly platform has also proven itself in the lifecycle management of product families. In 2015, one of SHL's pharma partners decided to perform lifecycle management on its PCSK9 autoinjectors for hyperlipidaemia. The project required two dosing formats in autoinjectors bearing communal industrial design and branding elements set by the pharma partner. A published usability study on the now-marketed high-dose, 2.0 mL format reported "no new product technical issues or no new safety concerns" compared with the 1.0 mL autoinjector format marketed previously. Study results like this affirm SHL's original findings on the Molly device's ease of use and highlight the platform device's applicability in metabolic therapy areas.[15]

Today, the metabolic space is experiencing extraordinary growth, with emerging clinical progress in mono-, dual- or triple-receptor agonists for obesity. The Molly autoinjector is well positioned to address emerging candidate compounds in this burgeoning market, offering quick-to-clinic device development options to support a pharma company's clinical trial strategy.[16]

SHL'S COMMITMENT TO PATIENTS

As SHL continues to collaborate with global pharma companies across various treatment areas, its commitment to providing the best possible experience for end users of its autoinjector technologies remains steadfast. As pioneers in self-injection technology, one of SHL's aims is to deepen its understanding of how autoinjectors activate, even in the softest injection sites.

> "With the obesity epidemic and the rising prevalence of cardiometabolic diseases, understanding adipose tissue function and distribution becomes critical."

Various studies have shown that body mass index (BMI) does not sufficiently reflect adipose tissue distribution, which includes visceral fat. With the obesity epidemic and the rising prevalence of cardiometabolic diseases, understanding adipose tissue function and distribution becomes critical. This is increasingly relevant for disease areas such as obesity and cardiometabolic diseases, where metabolic phenotypes could differ from other patient populations.[17–19]

To address this, the SHL research team conducted a series of soft tissue user (*in vivo*) studies, simulation (*in silico*) studies and physical test (*in vitro*) studies, providing a mechanistic view of the interactions between the autoinjector and human soft tissue during injection activation (Figure 3). The development of these *in silico* and *in vitro* models, which themselves represent challenging cases from the *in vivo* studies, goes above and beyond what is required in standard autoinjector testing methodologies, affirming SHL's commitment to end users. This study on autoinjector activation performance also confirms the safety and reliability of SHL's autoinjector technologies, even in more complex or heterogeneous patient groups.

ADDRESSING CARDIOMETABOLIC CHALLENGES WITH INNOVATIVE SOLUTIONS

The present obesity epidemic, affecting more than a billion people, underscores the urgency of addressing the various branching healthcare challenges related to cardiometabolic diseases. SHL Medical, a leader in self-injection solutions, is dedicated to improving lives with its autoinjector technologies. With a proven track record of meeting the growing needs of the cardiometabolic market, SHL's Molly autoinjectors are poised to usher in a new era in cardiometabolic care. SHL is committed to responding with innovative solutions to meet emerging needs for specialised device technologies in future drug discoveries.

ABOUT THE COMPANY

SHL Medical is a solutions provider in the design, development and manufacturing of advanced drug delivery devices, such as autoinjectors and pen injectors. The company also provides final assembly,

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labelling and packaging services for leading pharmaceutical and biotech companies across the globe. With locations in Switzerland, Taiwan, Sweden and the US, SHL Medical has successfully built a strong international team of experts that develops breakthrough drug delivery solutions for pharma and biotech customers. These include advanced reusable and disposable injection systems that can accommodate large-volume and high viscosity formulations – and connected device technologies for next-generation healthcare.

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ABOUT THE AUTHORS

Lars Berger is an accomplished professional with over 30 years of international experience driving innovation and growth in the medical device and healthcare industries. As Senior Manager of Portfolio Strategy and Customer Solutions at SHL Medical, he focuses on building and optimising the product portfolio by identifying opportunities based on customer needs, technical limitations and regulatory requirements. He has previously led over 15 development projects for pharma companies including Johnson & Johnson and Sanofi, including pioneering advancements in diagnostics, drug delivery devices, disease management applications and software as medical devices. He holds a master's degree in Business Science from the University of Regensburg (Germany).

Eric Linvill received his PhD in Solid Mechanics from the KTH Royal Institute of Technology (Stockholm, Sweden) in 2017 and is currently a Senior CAE Engineer at SHL Medical. Dr Linvill has research and professional experience in understanding and modelling the mechanical behaviour of biological and synthetic polymers and the development of advanced, non-linear finite element (FE) simulation models.

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A new era in metabolic care

With the rising demand for cardiometabolic medications to be delivered in primary care settings, there is an urgent need to unburden healthcare systems through self-injection treatments. As a pioneer in self-injection solutions supporting metabolic diseases, SHL Medical aims to improve as many lives as possible with our autoinjectors. Join us as we shape a new era in metabolic care.

Enabling patients' independence.

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