Zacks Small-Cap Research

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Valeritas Holdings (VLRX-OTC)

VLRX: Revenue Growth Despite 50% Reduction in Sales Force, Seasonally Soft Summer Season

Based on blended DCF and P/S comp, we value VLRX at $12/share. Our 15-year DCF, which uses a 10.5% discount rate and 2% terminal growth rate values VLRX at $12/share. P/S using PODD as comp values VLRX at $10 - $11/share. Roche acquisition of Medingo in 2010 for $160M provides additional validation to our $12/share valuation.

Current Price (11/23/16)	$4.35
Valuation	**$12.00**

OUTLOOK

Valeritas' V-Go Disposable Insulin Delivery device is the only FDA-cleared mechanical basal-bolus (continuous-single dose) insulin delivery device. By closely mimicking the body's normal physiologic pattern of insulin delivery V-Go has demonstrated in clinical studies to be able to lower A1C levels with less insulin as compared to a typical regimen of multiple daily insulin injections, providing both economic and clinical benefits.

V-Go was also designed to overcome many of the issues related to poor patient compliance of traditional (i.e. needles and insulin pens) insulin therapy– which have been an impediment to improving patient outcomes. Available at retail pharmacies, established reimbursement and cost-neutral to pens should afford low needle/pen-to-V-Go switching hurdle.

VLRX's recently revamped, efficiency-focused marketing strategy is already paying dividends in the form of revenue and margin growth as well as substantially improved operating loss. The company will continue to systematically deploy this strategy in high-opportunity territories. Based on three valuation methodologies, we calculate fair value of VLRX at $12/share.

SUMMARY DATA

52-Week High	**$6.50**
52-Week Low	**$2.85**
One-Year Return (%)	**N/A**
Beta	**N/A**
Average Daily Volume (sh)	**1,787**
Shares Outstanding (mil)	**13**
Market Capitalization ($mil)	**$55**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**0**
Insider Ownership (%)	**N/A**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2016 Estimate	**N/A**
P/E using 2017 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**N/A,**
Type of Stock	**N/A**
Industry	**Med Products**
Zacks Rank in Industry	**N/A**

ZACKS ESTIMATES

Revenue
(in 000s of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2015					18,097 A
2016	5009 A	4885 A	4860 A	4879 E	19,633 E
2017					24,692 E
2018					37,793 E

Earnings per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2015					-$6.14 A
2016	-$1.48 A	-$1.09 A	-$0.72 A	-$0.76 E	-$3.98 E
2017					-$2.20 E
2018					-$1.64 E

Zacks Projected EPS Growth Rate - Next 5 Years % **N/A**

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WHAT'S NEW…

Q3 Results: ***Revenue Growth Despite 50% Reduction in Sales Force, Seasonally Soft Summer Season..***

Valeritas reported financial results for the third quarter ending September 30th. Results on both the top and bottom lines were well ahead of our estimates. Revenue, at $4.86M, was essentially flat from Q2 of this year, up about 3% from Q3 2015 and 11% better than our $4.39M estimate. We had anticipated a sequential drop due to the fact that the third quarter is typically relatively soft as a result of a seasonal dip in prescription volumes associated with summer holidays and vacations. Perhaps, even more impressive was the yoy growth given that the sales force was more than twice the size in the year-earlier period as compared to the most recent quarter.

On the earnings call (that we missed due to a time conflict) management attributed the relative strength in revenue to rather unexpected scant prescription attrition from the territories which they vacated under their recently implemented capital efficient sales and marketing strategy. As a reminder, in an effort to rapidly improve profitability Valeritas recently revamped their marketing strategy to one which now focuses more resources in territories with higher prescribing physicians. The sales force was trimmed from 63 field reps (covering 63 territories) at the end of 2015 to 28 (covering 28 high potential territories) at the end of Q1 of this year. These vacated territories have remained more vibrant than expected, shedding approximately only 10% of revenue and suggesting a high level of physician and patient stickiness to V-Go despite the lack of high-touch direct detailing.

The fruits of the more efficient sales strategy is also apparent in operating expenses, operating loss and cash burn. SG&A fell from $9.9M, or 209% of revenue, in Q3 2015 to $8.0M, or 165% of revenue in Q3 2016. Meanwhile, operating loss improved from $10.8M and $39.3M in the three and nine months ending 9/30/2015 to $7.7M and $25.4M in the 2016 comparable periods. And cash used in operating activities (ex-changes in working capital) fell from $33.4M in the first nine months of 2015 to $20.8M in the comparable period in 2016.

Management is guiding for Q4 and full-year revenue of approximately $5M and $19.5M – implying roughly flat sequential growth from Q3 to Q4 and ~8.5% growth for the full year 2016. Again – impressive given the ~50% reduction in the sales force since late 2015. VLRX expects double-digit sales growth in 2017.

Heading Into 2017: Incrementally Grow Sales Team, Layer In Additional Marketing…

The direct sales team averaged between 27 and 28 reps in Q3, which is where VLRX expects to end 2016. Recent revenue growth has been a combination of existing detailed accounts writing more prescriptions per physician as well as the aforementioned stickiness of vacated territories. Management's plan into 2017 is to further drive prescription volumes at existing physician relationships, which provides particularly profitable incremental revenue given the virtual lack of any related additional cost (save for product COGS). They also continue to expect to expand their existing footprint to additional high-prescribing physician territories and grow the sales force over the next three to nine months. We currently model a weighted average of an additional 10 – 15 reps through the end of 2017.

In June VLRX brought on a VP of Marketing who is heading some new marketing initiatives which will begin roll-out in the short term and will be, at least in part, aimed at their goal of increasing prescription volumes of existing accounts. Management also indicated on the call that this could possibly include some local direct-to-consumer campaigns which can be effective in circumventing physicians as the gatekeepers to recommending alternatives to traditional insulin therapies.

Despite what VLRX has said is positive physician feedback which has included improved patient outcomes such as lowered A1C levels, the novel nature of V-Go is still somewhat of a headwind to more widespread physician adoption of V-Go. As such DTC campaigns, which aim to prompt type 2 diabetics to inquire about V-Go to their physician that may have not otherwise offered it as an alternative to conventional insulin therapy, seem to make sense. And patient 'feedback', as measured by retention rates also appears to be positive. Management noted that prescription data indicates that approximately 40% of patients that start V-Go, remain on it after one year – which compares to ~20% - 30% with traditional needle/pen insulin therapy. And another vote of confidence in V-Go is that 10 million devices has been dispensed as of October.

We are maintaining our $12/share price target.

SNAPSHOT

Valeritas Holdings, Inc, (VLRX) went public via an alternative public offering, executing a reverse merger and raising $25.2M ($23.7M net) through private placement of ~5M common shares at $5/share. The transaction closed in early May.

Valeritas is headquartered in Bridgewater, NJ, with manufacturing and R&D operations in Shrewsbury, MA, is engaged in the development and commercialization of medical devices for the treatment of patients with type 2 diabetes. The company's flagship product, V-Go Disposable Insulin Delivery device, was the first insulin delivery device cleared by the FDA (under its Infusion Pump Initiative). It launched in the U.S. in the summer of 2012 and remains the only FDA-cleared mechanical basal-bolus (continuous-single dose) insulin delivery device. While Valeritas' commercialization ambitions are currently focused solely on the U.S. market, V-Go also carries the CE Mark, allowing it to be sold in Europe as well. The technology is protected by more than 30 U.S. and international patients with an additional 50+ patents pending.

V-Go consists of a small, disposable (replaced daily) cartridge which adheres to the patient's skin. The device enables patients to closely mimic the body's normal physiologic pattern of insulin delivery by releasing a single type of insulin at a continuous preset background, or basal, rate over a 24-hour period and on demand around mealtime, or bolus dosing. V-Go has demonstrated in clinical studies the ability to lower A1C levels with less insulin as compared to a typical regimen of multiple daily insulin injections.

Complications of type 2 diabetes includes vascular damage leading to eye disease, kidney disease, nerve damage and even cause death from heart attack and stroke. Per the Centers for Disease Control and Prevention (CDC), approximately 22M Americans are currently diagnosed with diabetes, ~20M of which have type 2. Prevalence of diabetes in the U.S. is on the rise, having grown at a CAGR of approximately 4% since 1980. In the Europe Union, about 30M people have type 2 diabetes.

While insulin therapy has proven to be highly effective in controlling A1C and reducing risk of diabetes-related complications, factors such as anxiety (including 'psychological insulin resistance') and reluctance towards starting insulin therapy among the insulin-naïve and dosing complexity, insulin tolerability, cost and lack of convenience among insulin-experienced patients has resulted in low compliance of traditional (i.e. needles and insulin pens) insulin therapy and been an impediment to improving patient outcomes. V-Go was designed to overcome many of the issues related to poor patient compliance.

V-Go's Value Proposition includes;

- supported by extensive clinical evidence database including nine published papers, 34 posters and ~700 patients studied
- V-Go looks to be the most competitive pump technology for type 2 market. Versus;
  - Electronic insulin pumps: V-Go is much less expensive and complex than electronic insulin pumps, which are still almost exclusively used for the type 1 diabetes market
  - Patch pumps: V-Go is the only mechanical basal-bolus patch pump with FDA clearance. Competitiveness of other patch pumps are compromised by lacking basal delivery (which effectively eliminates the proven benefits of continuous insulin therapy), high complexity and related cost, insufficient reimbursement and/or lacking FDA clearance
- eliminates burden of carrying around insulin delivery devices and embarrassment of injecting in public
- ease-of-use and user-friendliness can increase patient compliance to prescribed insulin dosing schedule
- available at retail and mail-order pharmacies
- available reimbursement under private insurance as well as Medicare Part D
- similar cost to patients and payers as widely used insulin pens

Approximately 29% of type 2 diabetics use insulin. Valeritas' initial target market is the ~5.8M Americans with type 2 diabetes who currently use insulin and, in particular, the ~80%[1] (i.e. 4.6M) of those individuals which have been unable to control their A1C levels. The company estimates this population represents a total annual market worth upwards of $15B.

V-Go experienced brisk uptake since its launch in 2012, much of which was fueled by awareness building and a burgeoning sales force. But the early success in the form of ramping revenue and V-Go prescriptions came at the expense of significant operating losses. The legacy sales model was relatively inefficient with

[1] 2011 Database analysis of 27,897 adult diabetes patients on insulin. Chen Y et al. Poster presented at the 2012 AACP Annual Meeting

little discernment between high and low performing territories in regards to the marketing budget and strategy. In an effort to rapidly improve profitability Valeritas recently revamped their marketing strategy to one which now focuses more resources in territories with higher prescribing physicians. The sales force was trimmed from 63 field reps (covering 63 territories) at the end of 2015 to 28 (covering 28 high potential territories) currently. This has had the effect of improving sales rep efficiency and reducing operating expenses while at the same time growing sales and increasing gross margins.

We expect opportunity for incremental productivity gains from the sales force with more complete implementation of the revamped marketing strategy and management's increased focus on efficiency (i.e. sales per rep). Efficiency gains will come from scoring more accounts within the relatively narrow focus footprint. Assuming Valeritas continues to reap benefits from the recently implemented efficiency efforts, the next step will be to incrementally expand the sales force towards other high prescribing territories. Valeritas' current expectations are that the current ~28-head outside sales force will increase by another 10 to 20 reps (i.e 38 - 48 total) in during 1H 2017 as they reestablish their field sales force in some of the previously deprioritized markets.

BACKGROUND

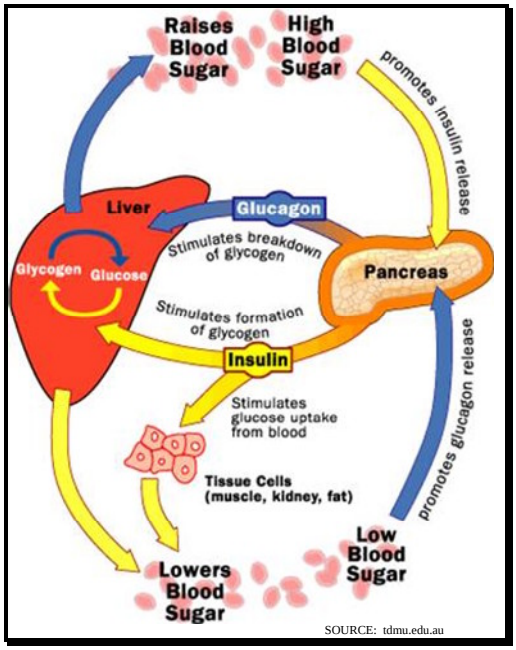
Insulin

Insulin is a hormone which is produced in the pancreas, the organ responsible for controlling sugar levels. Insulin's primary roles in the human body are to allow cells to use glucose (i.e. blood sugar) as energy as well as to aid in the storage of glucose for later use. It is the primary mediator of glucose levels, making sure blood sugar does not get too high or too low.

In healthy individuals, beta cells in the pancreas secrete insulin into the bloodstream in response to glucose, which will rise immediately after a meal. Insulin then attaches to cells and "unlocks" them, allowing for sugar to be absorbed by the cells which they then use as energy. At times when there is too much glucose in the blood (i.e. hyperglycemia), insulin helps to store the excess in the liver as glycogen. Another hormone, glucagon, works to convert the glycogen to glucose which is released into the bloodstream when blood glucose levels fall or when more energy is required.

Individuals with compromised insulin function (i.e. diabetics), including those with an inability to produce insulin (type 1 diabetes) or inadequate insulin production and resistance to insulin (type 2 diabetes), are unable to effectively use glucose as energy or to regulate it in the blood. This can lead to hyperglycemia which can result in a number of serious long-term complications.

Role of Insulin in the Human Body



Diabetes

Diabetes mellitus is a chronic metabolic disorder characterized by high blood glucose levels as a result of problems with insulin - where either the body is not making enough of this hormone or it is not effectively utilizing it. Chronically elevated blood sugar can cause serious complications and increase the risk of heart disease, eye problems including blindness, kidney disease, nerve damage (i.e. diabetic neuropathy) and dental diseases, among others potential problems. It is also the seventh leading cause of death.

Statistics…

According to the International Diabetes Federation, 415M people are currently affected by the disease worldwide (including ~30M in Europe) and this is expected to grow to 642M people by 2040. About one-half of those with the disease are unaware that they have it.

The CDC estimates that approximately 30M Americans, or about 9.5% of the total population, have diabetes. Of the 22M which are currently diagnosed with the disease, ~20M have type 2. Prevalence of diabetes in the U.S. is on the rise, having grown at a CAGR of approximately 4% since 1980. Around 1.7M new cases of diabetes among people 20 years or older and 200k cases among people younger than 20 years are diagnosed each year in the U.S. Prediabetes, in which blood sugar is abnormally high but not at a level to be considered diabetes, affects 37% of adults in the U.S. (~86M people), according to the CDC.

There are three main types of diabetes; type 1, type 2 and gestational:

Type 1 diabetes, which can be further delineated into 'immune-mediated' and 'idiopathic' forms, accounts for approximately 5% of all cases and is often referred to as juvenile diabetes as it typically develops early in life. Type 1 is characterized by autoimmune destruction of beta cells in the pancreas which are responsible for insulin production. The immune-mediated form, which accounts for the vast majority of type 1 cases, is caused by immune system T-cells attacking insulin-producing beta cells. The idiopathic form, as the name implies, is relatively rare with no known cause.

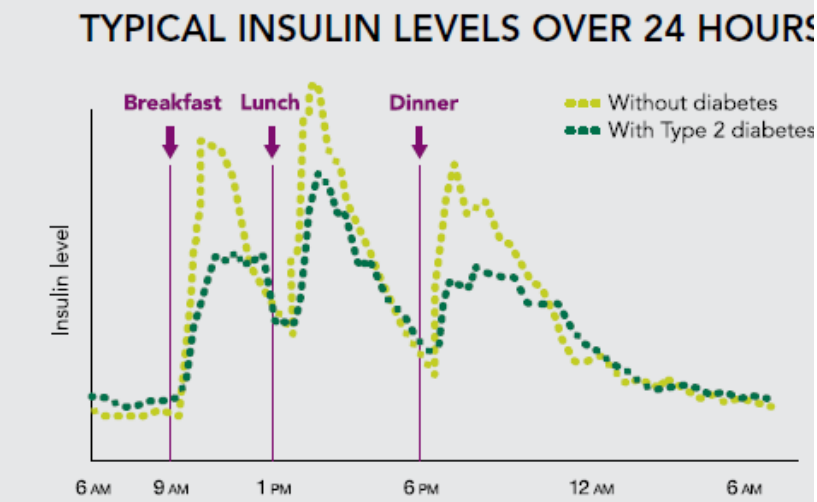
While many individuals with type 1 diabetes experience a 'honeymoon period' shortly following initial insulin therapy whereby the pancreas is able to produce some insulin, this is typically short-lived as the ability to produce insulin quickly deteriorates. Unlike type 2 diabetics, which oftentimes can improve their insulin function through diet and weight loss, most type 1 diabetics will lose the ability to produce any (or enough) insulin and will require insulin therapy for the rest of their lives.

Typical insulin therapy for type 1 diabetics includes multiple daily injections (MDI) via traditional syringe, insulin pens or insulin pumps. Normally two or more different types of insulin are used; rapid-acting, regular (or short)-acting, intermediate-acting, long-acting or a combination (pre-mixed) of these. The intermediate and long-acting insulin are basal doses used for maintenance of energy throughout the day while short-acting works as a bolus dose which is used for meals.

Type 2 diabetes, is often referred to as adult-onset diabetes although due to the obesity epidemic, it is becoming more common for children to be diagnosed with type 2 diabetes. Type 2 accounts for approximately 90% - 95% of all cases of diabetes. It is characterized by hyperglycemia due to the body's inability to properly use insulin. This is a result of a combination of resistance to insulin and insufficient insulin production.

Insulin resistance, which is believed to be a result of obesity and lack of sufficient exercise, refers to the body’s (muscle, fat and liver cells) failure to appropriately respond to insulin and inability to effectively absorb glucose from the bloodstream. This results in the pancreas increasing its insulin production. If the body can not keep up with the body's increased insulin demand, blood glucose levels rise which can lead to hyperglycemia and type 2 diabetes.

Unlike type 1 diabetics, most individuals with type 2 typically are able to produce some insulin and oftentimes will not need insulin therapy. In fact, only about 29% of diagnosed type 2 diabetics regularly use exogenous insulin. Type 2 diabetes, however, is a chronic condition that can get progressively worse if not properly controlled and therefore requires constant attention which usually includes some form of medical intervention.



SOURCE: Polonsky KS, et al. N Engl J Med. 1988;318(19):1231-1239

Along with a physical examination, **diagnosis of type 2 diabetes** involves measuring blood glucose levels. This includes HbA1C (A1C), fasting plasma glucose (FPG), random plasma glucose (RPG) and oral glucose tolerance (OGTT) tests.

A1C is a measure of average blood glucose for the past two to three months, FPG is a measure of blood glucose after not eating or drinking for at least 8 hours, RPG is glucose measurement at any time during hyperglycemia and OGTT measures blood glucose before and two hours following a glucose-laden drink.

The American Diabetes Association's (ADA) criteria for diagnosis of diabetes are any of the following;

- FPG $\geq$ 126 mg/dl (7.0 mmol/L). Fasting is defined as no caloric intake for $\geq$ 8 hours
- 2-hour PG $\geq$ 200 mg/dl (11.1 mmol/L) during 75-g OGTT
- A1C $\geq$ 6.5% (48 mmol/mol)
- Random PG $\geq$ 200 mg/dl (11.1/L) if patient has symptoms of hyperglycemia

The ADA's criteria for prediabetes (i.e. increased risk for diabetes) is;

- FPG = 100 - 125 mg/dl (5.6 - 6.9 mmol/L), defined as 'impaired fasting glucose' (IFG)
- 2-hour PG = 140 - 199 mg/dl (7.8 - 11.0 mmol/L), defined as 'impaired glucose tolerance' (IGT)
- A1C = 5.7% - 6.4% (39 - 46 mmol/mol)

Gestational diabetes occurs only during pregnancy in women that had previously not had the disease. It occurs in about 3% - 10% of pregnancies and usually goes away after the woman gives birth. It is caused by hormonal changes and weight gain brought on by pregnancy which results in insulin resistance. Gestational diabetes is typically treated with diet and exercise and, if needed, insulin.

V-Go Disposable Insulin Delivery Device: *Convenient, User-Friendly, Cost-Competitive…*

Valeritas' V-Go Disposable Insulin Delivery Device consists of a small, disposable (replaced daily) cartridge which adheres to the patient's skin, providing for both continuous (24 hour) as well as bolus subcutaneous administration of insulin. By more closely mimicking the human body's normal insulin delivery patterns V-Go has demonstrated in clinical studies the ability to lower A1C levels with less insulin as compared to conventional dosing using multiple daily insulin injections. And it does so with greater convenience, lack of restriction of daily activities (can even be used while swimming and exercising), user-friendliness and with simple meal-time dosing by taking a fixed number of clicks at each meal (i.e. low complexity). Small (2.4"x1.3"x0.5" and weighing 0.7oz when empty), discrete and worn under clothes, it frees the user from any anxiety of injecting in public and the need to carry around needles, insulin vials or other supplies. Relative to cost, V-Go is competitive to insulin pens.

V-Go Disposable Insulin Delivery Device

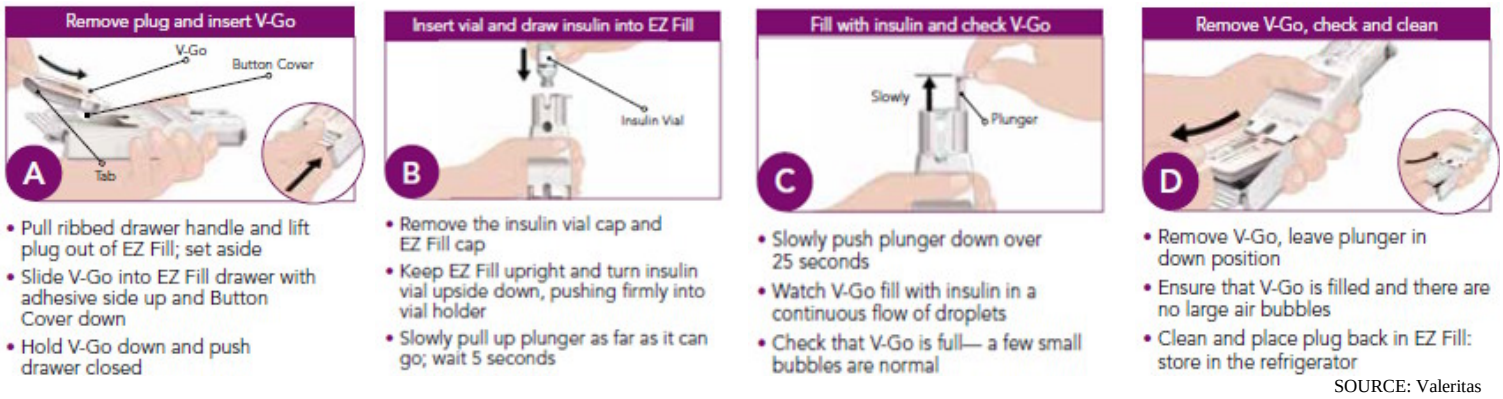


SOURCE: Valeritas

Operating Instructions: "Fill, Wear and Go"…

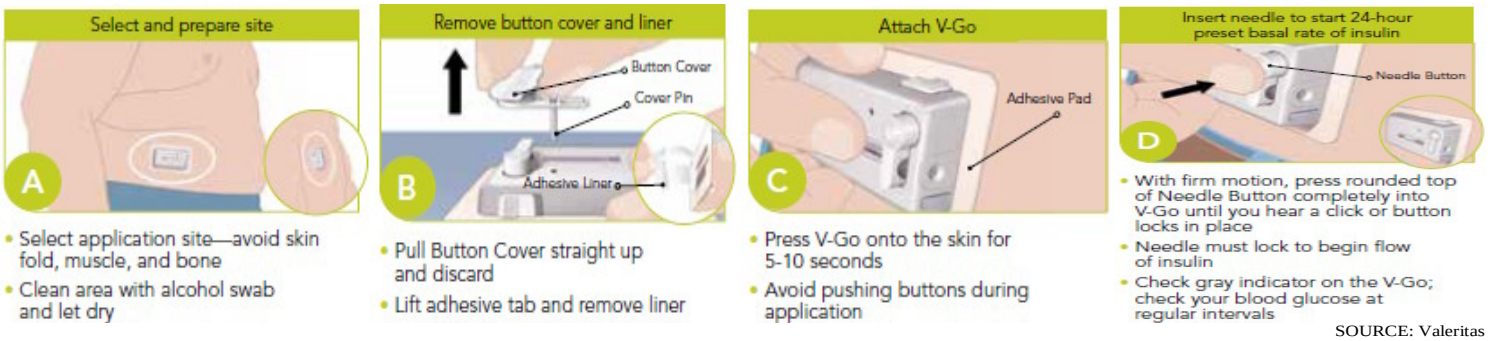
V-Go was specifically designed for simple and easy administration and to eliminate as much of the physical and mental burden of insulin therapy as possible. By doing so V-Go addresses most of the psychological issues related to initial adoption of insulin therapy among insulin naïve (i.e. psychological insulin resistance) and continuing use among the insulin-experienced.

1) Fill: A U100 fast-acting insulin is used with V-Go. Eli Lilly's (LLY) Humalog (insulin lispro, rDNA origin) and Novo Nordisk's (NVO) NovoLog (insulin aspart, rDNA origin), which are sold in vials and also used in these manufacturers' insulin pens, have been tested and been found to be safe with the device. Filling a new V-Go each day with insulin, using Valeritas' proprietary EZ Fill, takes only a few minutes. EZ Fill is designed for 30-day use and a new one is provided with the monthly V-Go subscription.



SOURCE: Valeritas

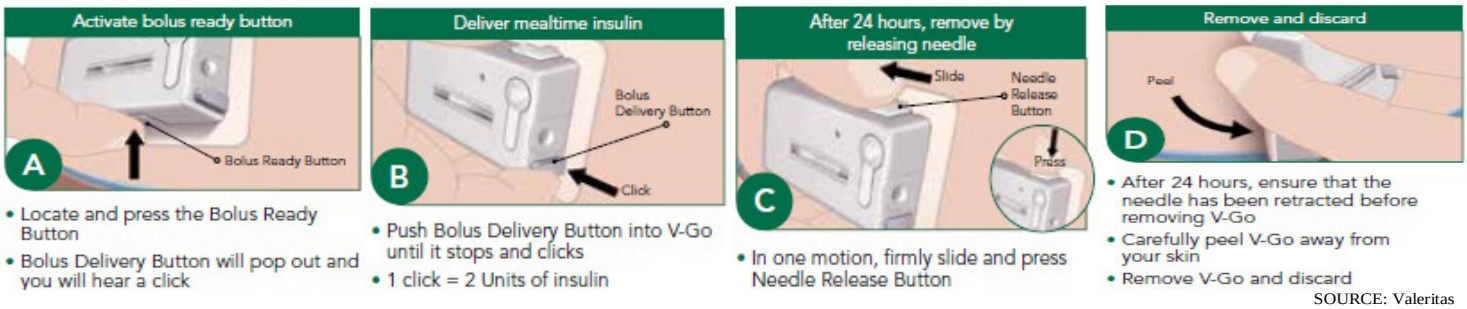
2) Wear: After V-Go is filled with insulin, the user removes a liner to expose an adhesive strip, places the cartridge on a flat part of the stomach or back of the arm and inserts the needle with a button push which also starts the flow of insulin. (See below for description of the insulin delivery technology).



SOURCE: Valeritas

3) Go: Other than a button push for bolus dosing at meal time, the user is now free from any other insulin responsibilities for the day. This is in contrast to the hassle of toting insulin supplies and needing to inject multiple times per day via traditional needle and syringe or insulin pens. And by closely mimicking

the human body's normal insulin delivery patterns with a continuous flow of insulin, V-Go addresses the peak and duration issues associated with conventional basal-bolus injections. After 24 hours (V-Go stays on while asleep) the users presses a button to release the needle, peels off and discards the device and repeats the process.



SOURCE: Valeritas

Regulatory Clearance, Models, Indications, Reimbursement, Intellectual Property…

V-Go received **FDA 510(k) clearance** in December 2010 as a Class II device. V-Go is a next-generation of the BioValve Insulin Delivery System (prior to being spun off in 2006, Valeritas was a wholly-owned subsidiary of BioValve) which was cited as the predicate device in the FDA filing.

V-Go is available as a 30-day supply and in **three different models** based on patient weight and insulin needs. 'V-Go 20' is **indicated for** continuous subcutaneous infusion of 20 Units in one 24-hour time period (0.83U/hr) and on-demand bolus dosing in 2-unit increments (up to 36 units per one 24-hour time period) in adult patients requiring insulin. The other two models are similarly labeled with the exception that 'V-Go 30' and 'V-Go 40' are indicated for use of 30 (1.25U/hr) and 40 (1.67U/hr) units of insulin, respectively, over 24 hours.

As each bolus delivery equals two units of insulin it is not recommended for people that require lower bolus doses due to the potential for hypoglycemia. It is also not recommended for those that require regular adjustments to basal insulin in a 24 hour period. However, it is estimated that these three models, which allow for up to 56, 66 and 76 units of insulin in a 24 hour period, meets the insulin requirements of approximately 70% of all type 2 diabetics.

A patient must obtain separate prescriptions for the V-Go device and the fast acting insulin that is used in it. As V-Go is a disposable (as opposed to reusable) insulin delivery device, it is covered under Medicare Part D (i.e. prescription drug benefit). Commercial insurers also typically cover V-Go under the pharmacy benefit. **Valeritas estimates that plans covering 70%+ of commercial and 60%+ of Medicare Part D lives in the U.S. provide reimbursement for V-Go**.

The company notes that over 90% of V-Go prescriptions have been filled at retail pharmacies since its launch. This is significant because diabetics are used to the convenience of filling insulin prescriptions at the pharmacy. So pharmacy access to V-Go allows a patient easy transition from needles and pens to V-Go.

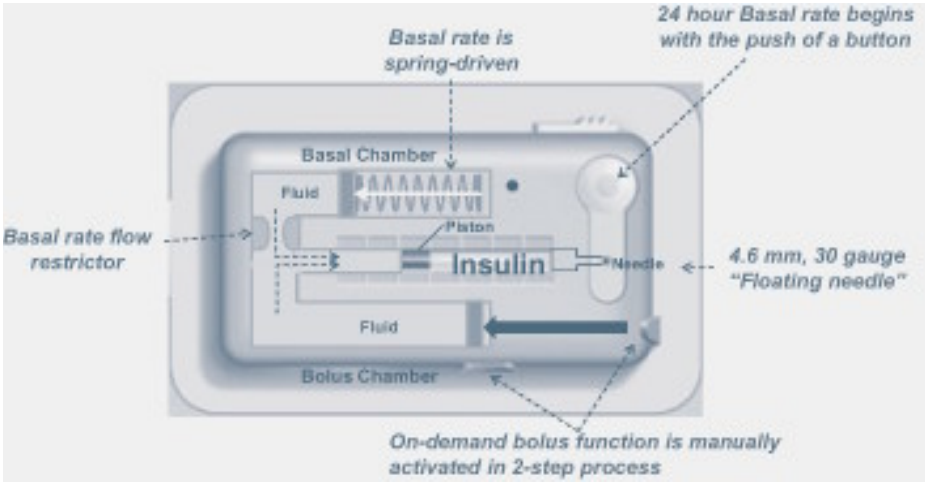
V-Go option	Preset basal rate	+	On-demand bolus dosing	=	Total available insulin
VGO® 20 DISPOSABLE INSULIN DELIVERY	20 Units/24 hr (0.83 U/hr)	+	Up to 36 Units in 2-Unit increments*	=	56 Units
VGO® 30 DISPOSABLE INSULIN DELIVERY	30 Units/24 hr (1.25 U/hr)	+	Up to 36 Units in 2-Unit increments*	=	66 Units
VGO® 40 DISPOSABLE INSULIN DELIVERY	40 Units/24 hr (1.67 U/hr)	+	Up to 36 Units in 2-Unit increments*	=	76 Units

SOURCE: Valeritas

The **patent** portfolio consists of 20 U.S. and 44 international issued patents and 13 U.S. and 46 international patents pending. The bulk of the patent portfolio relates to Valeritas' ***h*-Patch Controlled Delivery Technology Platform** which encompasses the technology surrounding the hydraulic drive for the basal-bolus delivery system.

Per Valeritas' current S-1 describing the *h*-Patch technology; "Once activated, our *h*-Patch system places a custom-formulated viscous fluid under pressure, which is separately compartmentalized and therefore designed not to come into contact with the active drug. Once pressurized, the fluid is forced through a flow restrictor that is designed to control the flow rate. After passing through the flow restrictor, the viscous fluid couples with and moves a piston in a cartridge that contains active drug. The viscous fluid continually pushes the piston, dispensing the drug at the prescribed preset basal rate through a needle into the patient's subcutaneous tissue. Bolus delivery on demand is similarly driven by viscous fluid dispensed from a separate side chamber, which allows a patient to dispense active drug in two unit increments through a user-activated bolus button. Our *h*-Patch basal drug delivery technology results in a simple, yet innovative, device that operates without complex controls or an infusion set."

h-Patch Technology



SOURCE: Valeritas S-1 filed July 22, 2016

Diabetes Management: *Diabetics' Resistance To Insulin Therapy Compromises Health*

Results from the Diabetes Control and Complications Trial (DCCT) conducted from 1983 - 1993 which followed over 1,400 people with type 1 diabetes helped to form the basis for ADA's recommendations in managing diabetes. The study compared intensive control of blood glucose to standard control of blood glucose on complications to diabetes. Intensive control was defined as keeping A1C levels as close to normal (i.e. of a non-diabetic) as possible.

The DCCT study along with the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study found that intensive blood glucose control reduces risk of;

- eye disease by 76%
- kidney disease by 50%
- nerve disease by 60%
- any cardiovascular disease event by 42%
- nonfatal heart attack, stroke or death from cardiovascular causes by 57%

While the DCCT and EDIC studies included only individuals with type 1 diabetes, other large studies including ACCORD, ADVANCE and VADT have shown that tight glucose control can reduce risk of complications with type 2 diabetics as well[2]. Based on the clinical evidence demonstrating better outcomes

[2] ACCORD: (n=10,000+) Action to Control Cardiovascular Risk in Diabetes. ADVANCE: (n=11,000+) Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation. VADT = (n=1,791) Veteran's Affairs Diabetes Trial

with stricter glucose control, ADA recommends the following targets (although certain individuals may require more customized targets);

- A1C $\leq$ 7%
- Preprandial (prior to a meal) plasma glucose of 80 - 130 mg/l
- Postprandial (1 - 2 hours following beginning of a meal) < 180 mg/l

Managing type 1 diabetes…

As type 1 diabetics do not produce insulin, they will need to constantly monitor their blood sugar levels throughout the day and take exogenous insulin for the rest of their lives. Typical management of type 1 diabetes includes;

- healthy diet and exercise
- check blood glucose levels with glucometer four to eight times per day
- multiple daily insulin injections
  - initially may start with two injections/day of two different insulin types but usually increases to three to four injections/day of different insulins
  - timing of injections, particularly as it relates to meals, is critical for proper glucose control
  - as type 1 diabetics exogenous insulin needs can be relatively complex throughout the day (which can include high, pre-breakfast morning glucose levels) use of different insulins including rapid-acting, regular-acting, intermediate-acting, long-acting or a combination (pre-mixed) of these is usually employed
- type 1 diabetics may also be prescribed other medicines to help control blood sugar including injectable pramlinitide, a synthetic form of amylin. Amylin, which slows gastric emptying thereby keeping blood glucose low, is also compromised in type 1 diabetics

Managing type 2 diabetes…

As most type 2 diabetics produce some amount of insulin, most do not require regular exogenous insulin therapy - at least not initially. First line therapy typically consists of diet and exercise. As the disease progresses (i.e. insulin resistance increases and/or insulin production declines) the next line of treatment to control blood sugar often involves once-daily oral medicines to; stimulate insulin secretion (sulfonylureas and meglitinides), decrease glucose production (biguanides), improve insulin action (thiazolidinediones) and directly lower A1C (DPP-4 and SGLT2 inhibitors).

If more aggressive therapy is required to control blood glucose, multiple oral medicines as well as injectable glucagon-like peptide-1 receptor agonists (GLP-1), which stimulate the release of insulin from the pancreas, may be used. The most severe stages of type 2 diabetes, when most or all other therapies have been exhausted, will include the use of insulin - either alone or in combination with one or more other therapies.

According to the CDC, approximately 29% of diabetics use insulin which includes 14% that use insulin alone and almost 15% which use insulin plus some form of oral medication. Among type 2 diabetics in the U.S., this equates to approximately 5.8M people that use insulin, including 2.8M that use insulin alone.

Type 2 diabetes insulin therapy typical follows a progression based on severity…

- initially this may include once-daily injection of a long-acting basal insulin
- as 82% of type 2 diabetics fail to control A1C with only basal insulin, most will progress to 'basal+1' or premixed insulin. This consists of either a daily injection of basal insulin plus one injection of fast-acting (bolus) insulin prior to the largest meal of the day or premixed insulin injections prior to breakfast and dinner
- if basal+1/premixed fails to control A1c the next step is MID's which may consist of one or two injections of long-acting insulin plus bolus injections prior to all meals

Despite the proven ability of insulin therapy to control blood glucose, it does have some **drawbacks**. Along with psychological aspects which cause patient angst (which we discuss below), there are physiological issues with insulin therapy as well. Exogenous insulin absorption in the body can be irregular, particularly when not delivered continuously. This means bolus dosing, if not timed correctly, can result in hyperglycemia immediately following meals and hypoglycemia later in the day while basal dosing can show a peak glucose-lowering effect and not last the entire day. And while insulin analogs (as opposed to human

insulin) have been developed to address these issues, they have not fully eliminated the peaking and duration problems.[3]

Effective Management Critical for Better Outcomes…

For non-diabetics, a normal A1C level is 5.7% or less. The ADA recommends that diabetics keep their A1C at 7% or less as effective control of A1C is critical in minimizing risk of diabetes-related complications. This is true for both type 1 and 2 diabetes;

- The DCCT and EDIC trials, as noted earlier, showed that as compared to standard therapy (mean A1C = 9%), intensive therapy (mean A1C = 7%) reduced risk of; retinopathy by 76%, diabetic kidney disease by 50%, neuropathy by 60%, any cardiovascular disease event by 42% and nonfatal heart attack, stroke or death from cardiovascular causes by 57% in type 1 diabetics
- ADVANCE showed intensive A1C control (mean = 6.5%) as compared to standard-control (mean A1C = 7.3%) reduced incidence of combined major macrovascular and microvascular events, microvascular events and nephropathy in type 2 diabetics. Specifically, intensive control reduced combined major macrovascular and microvascular events by 10% primarily due to a 21% reduction in nephropathy as compared to standard control[4]
- Meta analysis of five controlled studies aggregating across more than 33,000 subjects comparing diabetes-related complications found intensive therapy (i.e. mean A1C was 0.9% lower vs. standard therapy) resulted in a 17% reduction in non-fatal myocardial events and 15% reduction of coronary heart disease events[5]
- UK prospective diabetes study (UKPDS) compared intensive therapy (median A1C = 7.0%) to standard therapy (median A1C = 7.9%) in 3,642 type 2 subjects. Found incidence of complications was significantly associated with glycemia. Each 1% reduction in updated mean (i.e. mean of baseline and yearly measurements) A1C was associated with decreased risk of 21% related to any endpoint or death related to diabetes, 37% related to microvascular complications and 14% related to myocardial infarction[6]

Patients Often Reluctant to Begin Using Insulin…

While most type 2 diabetics at any given time are not using insulin, due to the progressive nature of the disease the majority of people who have type 2 diabetes will require exogenous insulin to control A1C within 9 years of initial diagnosis[7].

While insulin therapy has proven to be highly effective in controlling A1C and reducing risk of diabetes-related complications[8,9], patient anxiety and reluctance towards starting insulin therapy has been an impediment to improving patient outcomes. In fact recent findings have indicated that more than 25% of patients refuse insulin therapy when it is prescribed. And of those insulin-naive patients that do fill their first prescription, 26% don't obtain a refill[10] and as few as 29% may continue to take insulin just 12 months after their initial prescription[11].

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[3] Sanne G. Swinnen, MD, Joost B. Hoekstra, PHD, and J. Hans DeVries, PHD. Insulin Therapy for Type 2 Diabetes. Diabetes Care. 2009 Nov; 32(Suppl 2): S253–S259.

[4] ADVANCE Collaborative Group (Dr. Anushka Patel, et al.). Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med 2008;358:2560-72.

[5] Ray KK, Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D, Erqou S, Sattar N. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet. 2009 May 23;373(9677):1765-72. doi: 10.1016/S0140-6736(09)60697-8.

[6] Irene M Stratton, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405

[7] Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA. 1999 Jun 2;281(21):2005-12.

[8] The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329:977–986

[9] UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet. 1998;352:837–853

[10] Karter AJ, Subramanian U, Saha C, et al. Barriers to insulin initiation: the translating research into action for diabetes insulin starts project. Diabetes Care. 2010;33:733–735. doi: 10.2337/dc09-1184.

[11] Cooke CE, Lee HY, Tong YP, Haines ST. Persistence with injectable antidiabetic agents in members with type 2 diabetes in a commercial managed care organization. Curr Med Res Opin. 2010 Jan;26(1):231-8. doi: 10.1185/03007990903421994.

Several studies have found that much of the pushback from diabetics to insulin therapy relates to psychological reasons (the problem is so widespread and well documented that there is even a term for it, 'psychological insulin resistance') including; lack of confidence in being able to properly self-administer insulin shots, feel it would restrict everyday activities and embarrassment. Below we cite two of many studies that are in the public domain…

- A study by WH Plonsky[12], et al published in Diabetes Care (October 2005) surveyed 708 type 2 insulin-naïve diabetes patients attending diabetes conferences. Initial questionnaire assessed whether they were willing or unwilling to begin insulin therapy and also rated patients on a six point scale how strongly they agreed or disagreed with each of nine items relating to why they may be hesitant to begin insulin therapy. Results found that;
  - 28% were not willing to take insulin
  - most frequently cited negative beliefs about insulin therapy was
    - its permanence (45%)
    - restrictiveness of daily activities (45.2%)
    - hypoglycemia (43.3%)
    - personal failure and low self-efficacy (43.3%)
  - largest differences between those willing to take insulin and those unwilling to do so were
    - personal failure
    - low self-efficacy
    - anticipated pain
    - lack of fairness

Table 1—*Attitudes about insulin therapy, unwilling vs. willing subjects*

	Unwilling	Willing	Total	P*
Expected harm: Insulin therapy can cause problems, such as blindness	16.7	8.0	10.1	0.005
Illness severity: Taking insulin means my diabetes will become a more serious disease	46.7	35.4	38.1	0.000
Restrictiveness: Insulin therapy would restrict my life; it would be harder to travel, eat out, etc.	56.1	41.6	44.8	0.000
Lack of fairness: I've done everything I was supposed to; if I had to do insulin therapy, it just wouldn't be fair	41.5	21.9	26.8	0.000
Anticipated pain: I couldn't take the needle every day; it would be just too painful	50.8	30.2	34.7	0.000
Problematic hypoglycemia: Insulin therapy might cause serious problems with low blood sugar	49.3	37.9	40.6	0.021
Low self-efficacy: I'm not confident I could handle the demands of insulin therapy	58.1	39.7	43.9	0.000
Personal failure: Insulin therapy would mean I had failed, that I hadn't done a good enough job taking care of my diabetes	55.0	33.6	38.4	0.000
Permanence: Once you start insulin, you can never quit	53.1	42.6	44.9	0.000

Data are percentages of subjects who agree (either mildly, moderately, or strongly) with each barrier. *P values compare differences between willing and unwilling subjects.

SOURCE: Plonsky et al. Psychological Insulin Resistance in Patients With Type 2 Diabetes DIABETES CARE, VOLUME 28, NUMBER 10, OCTOBER 2005

- A systematic review of 25 articles related to barriers to starting insulin, published in 2015 in the International Journal of Clinical Practice, identified the main patient-related barriers to beginning insulin therapy were fear of pain and injection (n=18), concerns about side effects of insulin (n=12), perception that insulin indicated end-stage of diabetes (n=11), inconvenience (n=10), difficulty in insulin administration (n=7), punishment (n=7) and stigma and discrimination (n=7)[13].

Psychological Insulin Resistance Increases Risk of Complications…

With just 74% of insulin-naïve type 2 diabetics refilling their first prescription and only 29% still using insulin just 12 months after their first injection, there is an obvious reluctance of first-time users to begin insulin therapy due in large part to psychological barriers. Reluctance to begin insulin injections often results in a lag between the optimal point that a particularly patient should begin insulin therapy and when it actually

[12] WH Polonsky, et al. Psychological Insulin Resistance in Patients With Type 2 Diabetes. Diabetes Care, Vol 28, No 10, Oct 2005

[13] Ng CJ, Lai PS, Lee YK, Azmi SA, Teo CH. Barriers and facilitators to starting insulin in patients with type 2 diabetes: a systematic review. Int J Clin Pract. 2015 Oct;69(10):1050-70. doi: 10.1111/ijcp.12691. Epub 2015 Jul 6.

happens. This can have significant adverse consequences as the patient is unnecessarily exposed to high glucose levels for potentially significant amounts of time.

- Ioanna Zografou, et al.[14] retrospectively looked at 500 type 2 diabetes patients who started insulin therapy over a 9.5 year period between the years 2001 and 2011 to determine the time to insulin initiation, the glycemic burden that the patients are exposed to prior to conversion to insulin and their A1C level at that time and then one year later. What they found was that median A1C was 10% when insulin therapy was first initiated, was 8.8% six months prior to initiation and 8.3% 12 months prior to initiation. Further, patients spent a median period of 49 months with A1C > 7% (ADA's recommendation is A1c at or below 7%), 25 months with A1C > 8% and 10 months with A1C > 9%. Following 12 months of insulin treatment, A1C fell 1.8%.
- A. Rubino, et al retrospectively looked at 2,501 type 2 diabetes patients who had A1C $\geq$ 8% (i.e. the level in which it is determined oral glucose-lowering agents or OGLA are no longer effectively controlling blood glucose). The goal was to estimate the time to insulin initiation not well controlled by OGLAs. They concluded that if all patients were followed for five years that 25% would initiate insulin within 1.8 years of OGLA failure (i.e. A1C $\geq$ 8%) and 50% would initiate within 4.9 years.

The reluctance of many diabetics to begin insulin therapy, due in large part to psychological resistance, likely plays a significant part in the enormous lag (as long as almost 5 years in many cases) between when diabetics need insulin therapy and when they first receive it. This delay in initiation of insulin therapy puts diabetics at greater risk of complications given the overwhelming evidence (discussed earlier) of correlation between A1C and complications including retinopathy, kidney disease, cardiovascular events and neuropathy.

We believe that while some largely anxiety-driven issues (such as 'personal failure', 'lack of fairness' and 'permanence') that are hindering patients' uptake of insulin therapy may be overcome with better education from health care providers[15], administration (i.e. insulin-delivery related) issues such as 'low self-efficacy', 'restrictiveness' and 'pain' are likely best addressed with more patient-friendly insulin delivery devices.

Adherence Low Among Insulin-Experienced As Well…

Adherence to recommended insulin dosing regimens is not just a problem with insulin-naïve diabetics, it is also an issue with those that are experienced insulin users. Studies have shown that only approximately 62% of long-term insulin users adhere to physicians' recommended insulin dosing regimens.[16] Adherence becomes much worse, as low as 39%, when patients are prescribed both insulin and OGLAs.[17] And, as expected and similar to the insulin-naive, low adherence among the insulin-experienced is a significant predictor of A1C[18] and related complications.

While much of the low adherence to (and lag in starting) recommended insulin therapy among insulin-naïve type 2 diabetics can be explained by psychological insulin resistance, other factors including dosing complexity, insulin tolerability, cost and convenience all can play a part in adherence, or lack thereof, to insulin therapy among insulin-experienced diabetics.[19]

- Type 2 diabetes, being a disease that progressively gets worse, results in patients having to take more medicines and follow a dosing regime that is **more complex**. Complexity includes the need for the patient to adjust insulin dosing and insulin types (i.e. short-acting, rapid-acting, etc) throughout the day. As we noted earlier, studies have shown that as the number of drugs required to be taken and overall complexity increases, adherence decreases.

[14] Zografou I, Strachan MWJ, McKnight J. Delay in starting insulin after failure of other treatments in patients with type 2 diabetes mellitus. HIPPOKRATIA 2014, 18, 4: 306-309

[15] Linda M Hunt, PHD, Miguel A Valenzuela, BA and Jacqueline A Pugh, MD. NIDDM Patients' Fears and Hopes About Insulin Therapy: The basis of patient reluctance. Diabetes Care 1997 Mar; 20(3): 292-298. http://dx.doi.org/10.2337/diacare.20.3.292

[16] Cramer JA. A systematic review of adherence with medications for diabetes. Diabetes Care. 2004 May;27(5):1218-24.

[17] Yurgin NR, Boye KS, Dilla T, Suriñach NL, Llach XB. Physician and patient management of type 2 diabetes and factors related to glycemic control in Spain. Patient Prefer Adherence. 2008;2:87–95.

[18] Donnelly LA, Morris AD, Evans JM; DARTS/MEMO collaboration. Adherence to insulin and its association with glycaemic control in patients with type 2 diabetes. QJM. 2007;100:345–50.

[19] Luis-Emilio García-Pérez,corresponding author María Álvarez, Tatiana Dilla, Vicente Gil-Guillén, and Domingo Orozco-Beltrán. Adherence to Therapies in Patients with Type 2 Diabetes. Diabetes Ther. 2013 Dec; 4(2): 175–194.

Insulin pens, in which the dose can be simply adjusted with the twist of a dial, as well as premixed insulins have shown to partially address the complexity issue and improve compliance as compared with injecting via traditional syringes.

- ✧ While intensive insulin therapy has been found to effectively control A1C, certain individuals including older and severely obese patients have shown **less tolerance** to relatively high insulin dosing regimens. In some studies intensive insulin therapy was associated with higher mortality, weight gain and hypoglycemia. These patients are also less likely to adhere to recommended insulin therapy.
- ✧ Studies have shown that **cost** can be a factor in adherence including one in which participants listed it (i.e. cost) as the most significant factor affecting lack of adherence to their recommended type 2 medication regimen[20]. There is also a trade-off between cost and complexity relative to traditional syringes and insulin pens. While pens offer greater convenience, this usually comes with a much higher cost.
- ✧ **Convenience** can be a significant factor in adherence for type 2 diabetics given that many require several injections each day. Traditional syringe and insulin vial, while more cost effective, are relatively inconvenient and cumbersome to carry around and much more obvious when administering in public as compared to insulin pens. Studies have indicated that more convenient and private administration can positively influence adherence. Per U.S. Roper Diabetes Patient Market study, as much as 72% of type 2 diabetics which have been prescribed three or more insulin shots per day do not inject themselves when in public. Lack of convenience, complexity and embarrassment were all indicated as reasons.

V-Go: *Addresses Issues of Low Adherence, More Effective than Injections…*

Positive User Feedback…

In 2008 Valeritas conducted a 'user preference program' (UPP) for feedback on V-Go from physicians and patients related to their overall experience with the device. Participants included 31 patients and their 10 physicians who were asked to rank (1 - 10, higher = better) their impressions of certain parameters of V-Go. Participating patients used V-Go therapy for an average of 6.5 months. Questions related to; overall experience, ease of use, discreetness, comfort, recommend to family/friend and how helpful was the patient education.

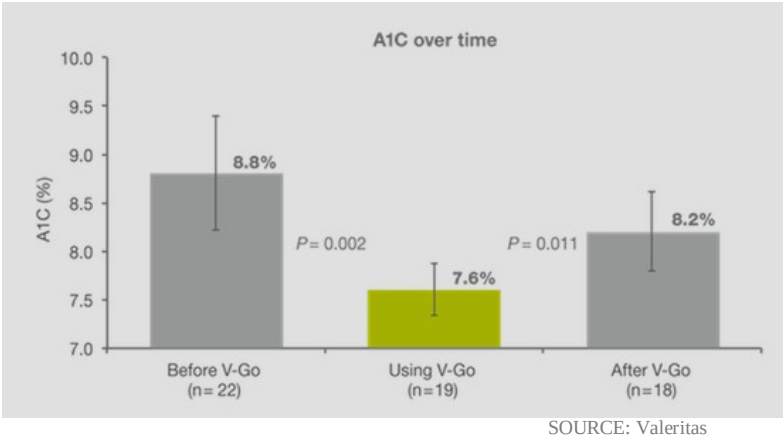
On all parameters average score ranged between 8.7 and 9.4. We think particularly noteworthy is that 'ease of use' and 'discreet', which studies have indicated are major factors for psychological insulin resistance, both averaged 9.3 (i.e. high) in this UPP study. Adherence to V-Go was also surveyed which showed patients adhered to the treatment approximately 98% of the time.

Clinical Data Shows V-Go Controls A1C, Utilizes Less Insulin

Results of several clinical studies which included more than 700 patients have indicated that V-Go may be able to control A1C better than traditional insulin injections at significantly lower insulin doses than basal or MDI regimens. Below we provide a summary of the larger data sets;

- **UPP:** the UPP study also included a retrospective analysis of glucose control of V-Go in 23 patients (22 type 2, one type 1)
  - o results were published in the journal Endocrine Practice in Sept/Oct 2012
  - o data collected prior to, after 12 weeks of, at the end of and 12 weeks after V-Go treatment
  - o results showed mean A1C improved from 8.8% prior to V-Go treatment to 7.6% (p=0.005) after 12 weeks of treatment
  - o when patients discontinued use of V-Go and switched to other therapies, average A1C went up to 8.2%
  - o no serious adverse events were reported during V-Go use and there was no difference in hypoglycemic events
  - o investigators concluded that improved A1c control with V-Go may be attributable to more efficient glucose lowering as well as better patient adherence to the therapy due to its simplicity

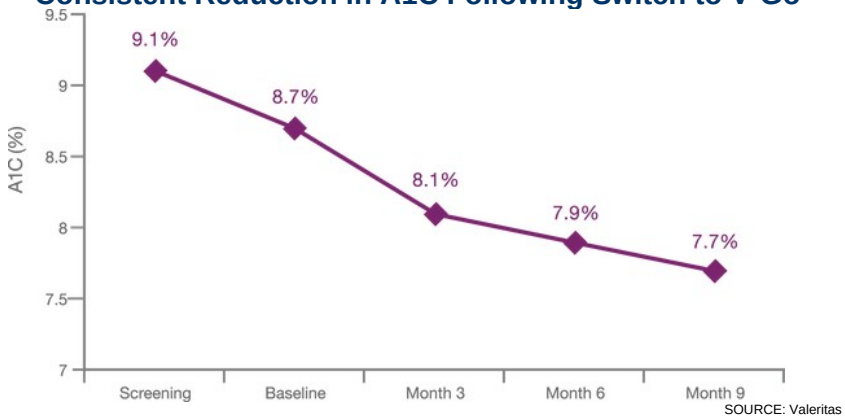
[20] Odegard PS, Gray SL. Barriers to medication adherence in poorly controlled diabetes mellitus. Diabetes Educ. 2008;34:692–697.



SOURCE: Valeritas

- **SIMPLE Study:** open label, multi-center study comparing change in A1C prior to and at the end of V-Go therapy in 89 type 2 patients on one or more daily insulin injections and not meeting A1C target of 7%. Patient population included those on basal, premix and MDI insulin regimens (regardless of oral diabetes medicine use) who were switched to V-Go therapy (V-Go 20, 30 or 40 based on physician's direction)
    - interim results of 40 patients through 6 months of treatment were presented in a poster presentation at the American Association of Clinical Endocrinologists 23rd Annual Scientific Congress in May 2014
    - mean change in A1C across all patients improved from 8.9% at baseline to 7.9% at month 6. The difference (1.0%) was highly statistically significant (p=0.001)
    - while the interim data did not show a reduction in total insulin dose (i.e. basal plus bolus) from baseline, it did show mean basal dose rate across all patients fell 27% from baseline (43.5 units/day) to month 6 (31.8 units/day). The basal dose reduction was most pronounced in patients on high basal doses (-33%) than on those on initial low basal doses (-13%)
    - a consistent reduction in mean A1C across all patients was observed through month 9 when patients switched to V-Go therapy (chart below)
    - few hypoglycemic events were reported and there was no change in body weight

Consistent Reduction in A1C Following Switch to V-Go

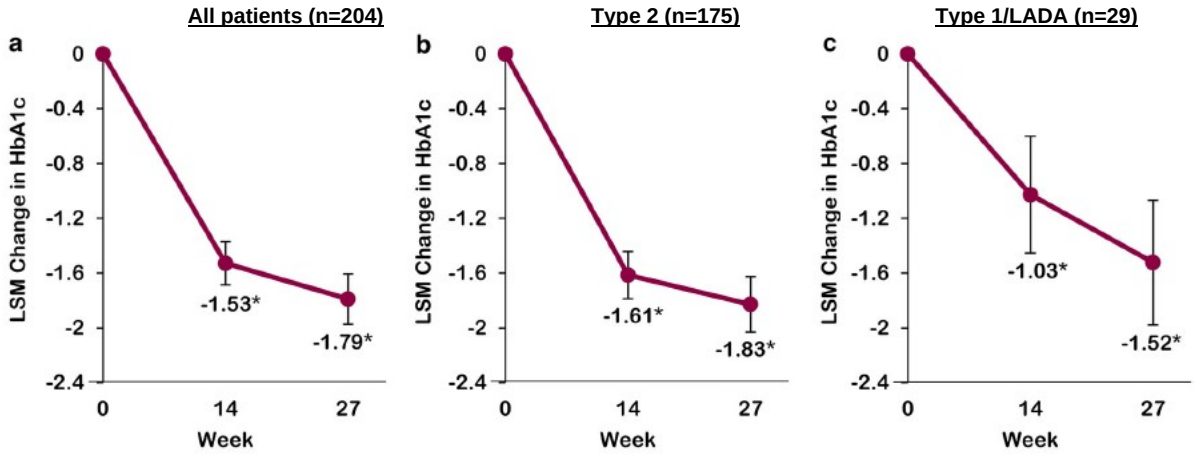


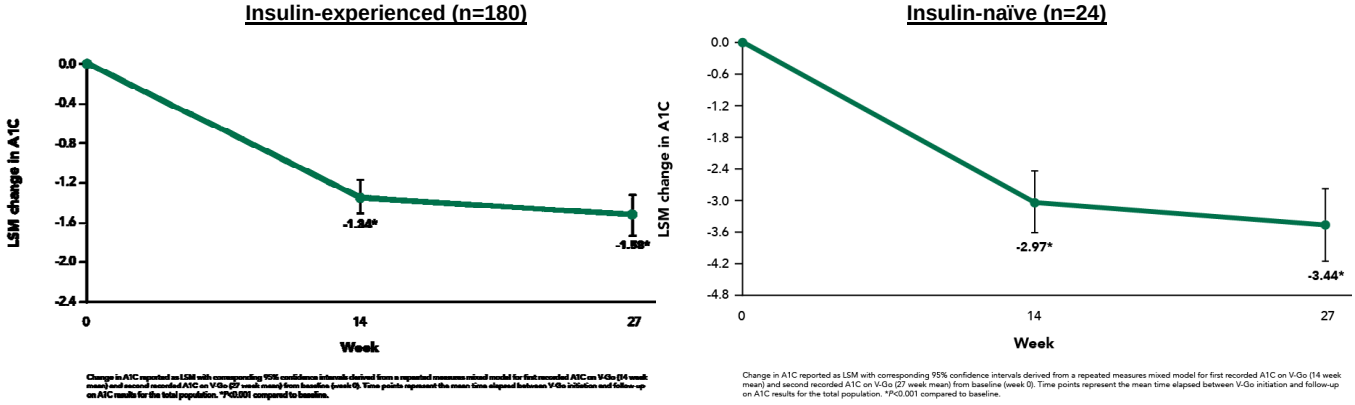
SOURCE: Valeritas

- **Diabetes America Study:** showed statistically significant reductions in A1C and insulin usage when patients switched from injections to V-Go. Retrospective analysis of 204 type 1 (and LADA) (n=29) and type 2 diabetes (n=175) patients which were either prescribed basal-bolus insulin therapy (n=180) or insulin-naïve (n=24), all with or without oral insulin medication, and which switched to V-Go
    - results were presented at the American Association of Clinical Endocrinologists' 24th Annual Scientific and Clinical Congress
    - average time to first and second follow-up visits were approximately 14 and 27 weeks, respectively

- results showed a statistically significant reduction in A1C after switching to V-Go at both 14 and 27 weeks in not only the entire population but also in all patient subsets (type 2, type 1/LADA, insulin-experienced and insulin-naïve) - charts below
  - all patients: A1C reduced 1.53% and 1.79% at 14 and 27 weeks, respectively
  - type 2: A1C reduced 1.61% and 1.83% at 14 and 27 weeks, respectively
  - type 1/LADA: A1C reduced 1.03% and 1.52% at 14 and 27 weeks, respectively
  - insulin-experienced: A1C reduced 1.34% and 1.58% at 14 and 27 weeks, respectively
  - insulin-naïve: A1C reduced 2.97% and 3.44% at 14 and 27 weeks, respectively
- subset (n=153) analysis also showed significant reduction in A1C in patients previously receiving MDI therapy (-1.2%) as well as basal insulin (-2.3%) after switching to V-Go
- in terms of insulin usage; insulin-experienced patients required significantly less insulin with V-Go. Total insulin doses were 33% - 41% (86-99 u/day vs. 58 u/day) lower than the prescribed baseline dose at 27 weeks while basal insulin rates were 39% - 46% lower (54-58 units/day vs. 33 units/day). The difference was highly statistically significant ($p<0.001$)
- a subset analysis (n=104) was done to evaluate insulin dose and A1C control among patients that had moderate baseline insulin dose (i.e. <100u/day) and high baseline dose (i.e. >100u/day) and were switched to V-Go. Results showed a statistically significant reduction in A1C and insulin use in both cohorts after 6 months. In addition, the reductions in A1C were similar between the two cohorts and both groups required a similar amount of insulin after switching to V-Go, despite significant differences in insulin requirements at baseline. This provides additional validation that V-Go provides administration of insulin that is more efficient for the body to use than injections
- there was no difference in reported hypoglycemic events across all patients

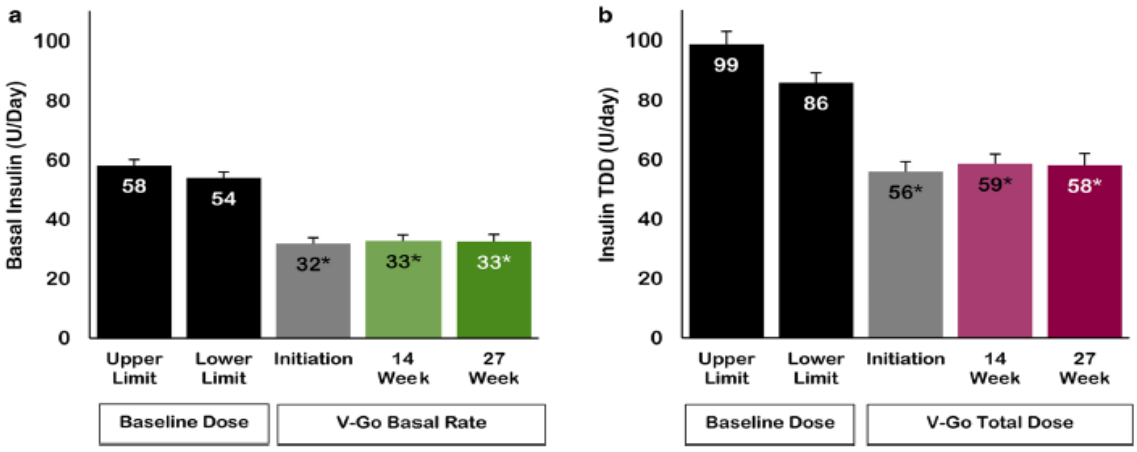
Statistically Significant Improvement in A1C When Switched to V-Go





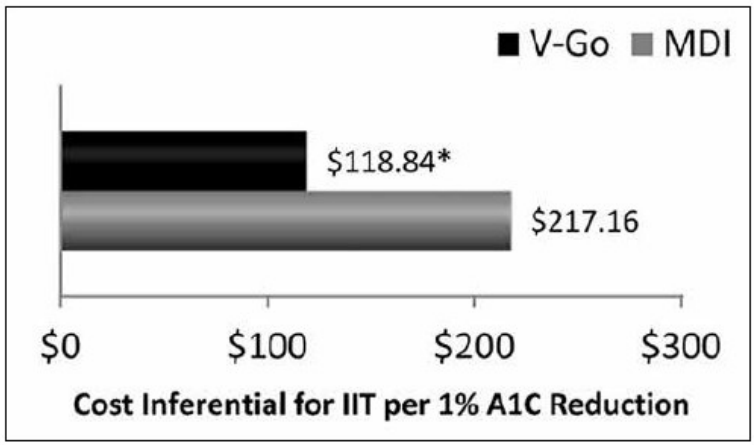
Change in A1C reported as LSM with corresponding 95% confidence intervals derived from a repeated measures mixed model for first recorded A1C on V-Go (14 week mean) and second recorded A1C on V-Go (27 week mean) from baseline (week 0). Time points represent the mean time elapsed between V-Go initiation and follow-up on A1C results for the total population. *P<0.001 compared to baseline.

Statistically Significant Reductions in Insulin Usage When Switched to V-Go



- **Diabetes America Comparative Study:** retrospective analysis of a subset (n=116) of the Diabetes America study population comparing glycemic control, insulin usage and cost of two types of intensive insulin therapy; V-Go therapy (n=56) and MDI (n=60), in type 2 diabetes patients inadequately controlled on basal insulin of oral anti-diabetes drugs.
    - results were published in June 2016 in Endocrine Practice
    - there were significant improvements in A1C in both groups from baseline. At 27 weeks A1C fell 1.98% with V-Go and 1.34% with MDI. The difference favoring V-Go of 0.64% is statistically significant (p=0.02)
    - in terms of insulin usage, V-Go patients used an average of 56 u/day compared to 78 u/day with MDI. The 28% difference is statistically significant (P<0.001)
    - a cost analysis was also done which showed that, due to in large part to lower insulin requirements, mean direct monthly pharmacy costs per patient were lower with V-Go ($235) than for MDI ($291)
    - in addition, an analysis was done to evaluate the cost of each treatment per 1% reduction in A1C. Results again showed V-Go was more cost efficient, costing on average $119 per patient compared to $217 with MDI for each 1% reduction in A1C

V-Go Much More Cost Effective Than MDI[21]



[21] Rosemarie Lajara, MD; Jaime A. Davidson, MD, FACP, FACE;Carla C. Nikkel, BS, RD, LD, CDE; Tracy L. Morris, PhD. Clinical and cost-effectiveness of insulin delivery with V-Go Disposable Delivery Device versus multiple daily injections in patients with type 2 diabetes inadequately controlled on basal insulin. Endocr Pract. 2016;22:726-735)

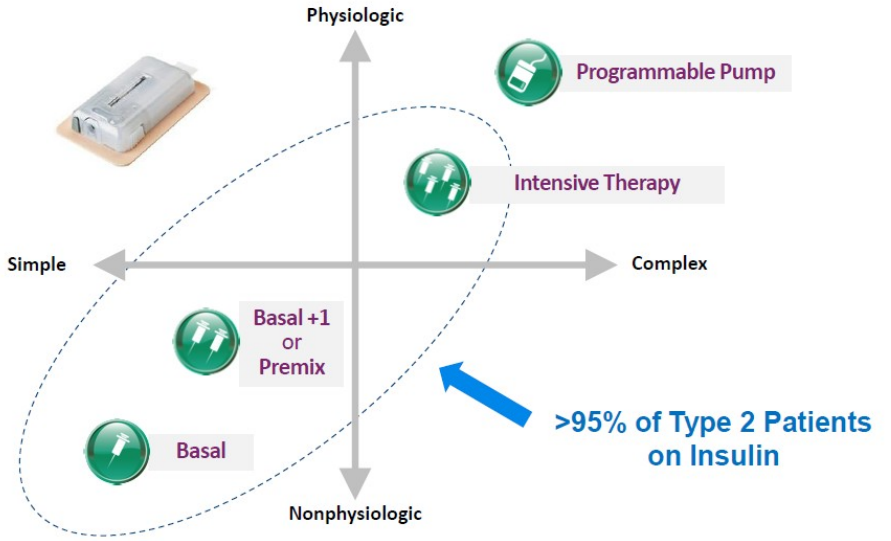
- **Results of Other, Smaller Studies Also Support Benefits of V-Go:** other, smaller studies have also been conducted showing similar benefits of improved A1C reduction and lower insulin use with V-Go. These include;
    - **Early Access Program (n=16):** after three months of V-Go therapy, patients' average A1C decreased 1.9% (9.3% to 7.4%). Clinicians reported a 22% decrease in insulin usage with V-Go
    - **UMass Clinical Evaluation (n=21):** patients switched from MDI to V-Go. Results, of the 14 evaluable patients, showed after 88 days of V-Go therapy A1C fell from 10.7% to 8.3% and total daily insulin doses fell from 119 units to 64 units. Both the reduction in A1C and insulin were statistically significant ($p<0.01$)
    - **Jones Center for Diabetes & Endocrine Wellness Clinical Evaluation (n=91):** type 2 diabetes patients switched from insulin therapy to V-Go. Mean A1C of the 69 patients that had at least one follow-up fell from 9.1% at baseline to 8.3% at follow-up. Mean total daily insulin doses fell from 76 units to 61 units.

V-Go Competitive Positioning: ***Easier, More Effective & Cost-Competitive vs. Other Insulin Delivery Methods…***

While insulin pens' popularity among diabetics can be largely attributed to their effectiveness in addressing some of the shortcomings of traditional needle injections such as greatly reducing the required skill and providing somewhat greater discretion, they still do not manage the non-physiological nature and related peaks and duration issues associated with basal and bolus insulin injections. And while pens are less bulky than needles and insulin vials, they also do not fully eliminate the burden of patients having to carry around their insulin supplies.

Supported by clinical studies demonstrating V-Go's ability to more effectively control A1C by closely mimicking the human body's normal insulin patterns and high experience-related scores from patients and physicians, Valeritas is positioning V-Go as a more effective, user-friendly and less burdensome alternative to conventional insulin delivery methods including traditional needle injections and insulin pens. And at a cost that is approximately the same as insulin pens, broad (and growing) reimbursement coverage and retail pharmacy accessibility, there may be few if any meaningful hindrances to a type 2 diabetic's seamless transition from pens and needles to V-Go.

V-Go: Easier and More Effective Than Insulin Injections



SOURCE: Valeritas

Cost competitive to pens…

Not only has V-Go therapy shown to be more cost-efficient than MDI for every 1% reduction of A1C, which benefits payors, it is also cost-neutral to patients using insulin pens. Using assumed co-pay of $62 ($31 each for basal and bolus pens) for insulin pens and $11 for pen needles under Tier 2 formulary coverage, a

patient using insulin pen therapy will spend ~$73/month. This is roughly equal to average co-pays of V-Go therapy which is $62 ($31 for V-Go device plus $31 for insulin vials) under Tier 2 and $84 ($53 for V-Go device plus $31 for insulin vials) under Tier 3 coverage.

Other Insulin Therapies…

While approximately 95% of type 2 diabetics that use insulin administer it with either needles or pens, there are other alternatives including jet injectors, inhaled insulin, insulin pumps and insulin patch pumps.

- **Jet injectors** use high pressure to push insulin through the pores. While injectors offer an alternative to needle delivery which may appeal particularly to individuals with needle phobia, they may actually cause more pain than needles. Other drawbacks include a relative high cost and the potential for uneven insulin delivery due to injectors not always pushing the complete dose through the skin
- **Inhaled insulin** may provide another alternative to needles but it also has drawbacks. These include a much lower bioavailability compared to subcutaneously delivered insulin requiring higher doses. Additionally, oftentimes patients will still need to inject long-acting insulin. And finally, inhaled insulin's long-term effects on the pulmonary system are not yet known
- **Insulin pumps** are mostly used by type 1 diabetics given these patients' relatively complex and high insulin needs. Insulin pumps allow for more precise insulin delivery as compared to injections and when integrated with continuous glucose monitoring (CGM), can automatically adjust insulin dose. Electronic pumps are typically worn on the patient's belt or in the pocket and deliver both basal and bolus insulin via a tube which connects the pump to the body. The insulin is delivered via a cannula which is inserted under the skin. Pumps' programmability and ability to adjust insulin dose provide for more effective A1C control versus MDI. Disadvantages include that electronic pumps are relatively very expensive, costing upwards of $5,000 and complex, requiring significant patient and physician education. Moreover, many patients find them unwieldy. For these reasons, insulin pumps are typically only used by type 1 diabetics.
- **Insulin patch pumps** are the category that V-Go belongs to. This is a newer category of insulin delivery devices. These aim to replace needles and pens but with less complexity and cost and more user-friendliness than electronic insulin pumps. A specific comfort advantage of patch pumps is that unlike electronic insulin pumps, they do not use tubes to deliver the insulin from an external pump. In addition to insulin pens and traditional insulin injections, insulin patch pumps, which are marketed to both type 1 and type 2 diabetics, represent what we believe to be the most closely related competition to V-Go. This includes Johnson & Johnson's (NYSE: JNJ) OneTouch Via and Insulet Corp's (NSDQ: PODD) OmniPod System, the only other patch pumps currently cleared for sale in the U.S.
    - **OneTouch Via** (formerly known as Calibra Finesse) mealtime, on-demand insulin delivery system has yet to launch despite receiving FDA clearance in 2010. It is also CE Marked. Acquired by J&J in 2012, it is the device that is most similar to V-Go in that it is mechanical, does not require a controller, is disposable and is marketed primarily for type 2 diabetes. Potential advantages of Finesse as compared to V-Go include its slightly smaller size (2"x1"x0.5" vs. V-Go at 2.4"x1.3"x0.5") and larger capacity (200 units vs. V-Go's 76 units) allowing it to be worn for up to three days (vs. one day with V-Go). A disadvantage is that, unlike V-Go, which delivers both basal and bolus doses, OneTouch Via provides only on-demand bolus doses (at the touch of two buttons). We view this as a significant competitive drawback of OneTouch Via given the clinical (such as greater A1C lowering efficacy) and other (such as less insulin used) benefits of continuous insulin delivery. It also means that OneTouch users on MDI must go through the extra step of manually injecting long-acting insulin (and tote those supplies). And finally, in terms of reimbursement and cost, a patient using OneTouch Via would have three co-pays, one each for the device, bolus insulin and whatever form of basal insulin they use. J&J has recently indicated that they expect to launch OneTouch Via in certain OUS markets in late 2016 and in the U.S. shortly afterwards.
    - **OmiPod System**, which launched in the U.S. in 2005 and in Europe in 2010, is somewhat of a hybrid between a traditional electronic pump and an insulin patch pump in that the patch is integrated with a wireless controller which is used to program automatic basal dosing. The user must also use the controller to deliver a bolus dose. The patch (or 'Pod'), at 2.05"x1.53"x0.57," is comparable in size to V-Go but differs in that it is uses a battery to electronically deliver the insulin. The controller, which is worn on the user's belt, measures 4.5"x2.5"x1.0" - about the size of a very thick smart phone. OmiPod, with an insulin capacity of 200 units, can be worn for up to three days. Disadvantages of OmniPod as compared to V-Go is its higher complexity, the need to carry the controller to administer bolus doses and at ~$640, it is relatively expensive. In addition, lack of Medicare/Medicaid coverage has been

cited as an impediment to greater uptake. OmniPod's additional functionality means that it is mostly marketed to the type 1 diabetes market and as such, we view it less of a near-term direct competitor to V-Go

- Other insulin patch pumps targeting the type 2 diabetes market include Solo patch and PaQ. **Solo** was developed by Israel-based Medingo and acquired by Roche (RHHBY) in 2010 for $160M. Similar to OmniPod, it uses a separate controller to signal the electronic patch pump to deliver programmed basal and on-demand bolus doses. While Solo received FDA clearance in 2009, Roche has yet to make it available for purchase. If and when launched in the U.S., we think Solo's similarities to OmniPod mean it will have limited appeal to the type 2 market. **PaQ**, made by Swiss firm CeQur, received CE Marking in 2012 and is available in Europe. PaQ's disposable insulin reservoir, which can hold up to 330 units and can be worn for up to three days, attaches to a reusable infuser (i.e. patch). PaQ allows users to choose from up to seven preset basal rates (vs. three for V-Go). However, unlike V-Go's fully mechanical insulin delivery, PaQ uses an electronic messenger in its patch which could make it more expensive. While it is not currently available in the U.S., CeQur has indicated their intentions to seek FDA clearance.

OneTouch Via **OmniPod**



SOURCE: medgadget

OUTLOOK / VALUATION

Financial Model

Revenue grew to $18.1M in 2015, from $13.5M in 2014. The 34% revenue growth was a result of a combination of an 8% average price increase and growth in prescription volumes, the latter facilitated by territorial expansion. Based on prescription data Valeritas estimates there were approximately 92k V-Go prescriptions in 2015 and ~11.5k patients were using V-Go as of the end of that year. With manufacturing capacity of up to 16 million units (~530k 30-day Rx equal to ~$100M in revenue) at their Chinese contract manufacturer, Valeritas should be able to scale as quickly as they can increase order flow.

Our model assumes sales reps experience a largely linear improvement in productivity over the first several years after hire and average peak productivity per field rep in high prescribing territories is initially approximately 450 total prescriptions per month (and increases at a rate commensurate with market growth), which equates to V-Go revenue of ~$1.1M per year (using assumed net sales price of ~$200/Rx). The majority of our modeled revenue growth through 1H 2017 is from prescription growth due to productivity gains from the current (n=28) sales force. We also incorporate a modest contribution from an assumed incremental increase in the total size of the sales force as Valeritas begins to reprioritize some of the ~35 areas that were back-burnered within their revamped marketing strategy.

The relatively enormous size ($11B) of Valeritas' focused market coupled with the dearth of any directly comparable competitive products in the patch pump space means that adoption and prescription growth of V-Go could be swift and potentially only constrained by how quickly Valeritas can begin to detail and service new accounts. This will be dependent on effectively building out the sales and marketing infrastructure, which in-turn may be dependent on raising additional capital when needed.

Our longer-term revenue estimates assume continued productivity gains coupled with very incremental annual net growth of the field sales force, incremental price increases and market growth commensurate with diabetes industry market forecasts. We do not currently incorporate any assumed contribution from OUS markets nor any contribution outside of the insulin-experienced type 2 population with A1C not effectively controlled. Using those assumptions, our model indicates V-Go will generate approximately $110M of revenue (market share < 1%) by the year 2024, implying 8 year CAGR of ~24%. While this is arguably conservative, particularly if OmniPod which saw revenue grow from $13.4M in 2007 to $324M in 2015 (8 year CAGR of 49%) is used as a benchmark, we balance potential opportunity for steeper growth rates with that of execution risk and the expectation that VLRX's sales and marketing infrastructure remains relatively lean.

Expect margin expansion on volume growth…
Valeritas' recent sales and marketing restructuring was the result of less than effective deployment of personnel and capital. The cost cuts and revamped strategy has beefed up gross margins and significantly reduced operating losses. We look for gross margins to further expand over the long-term on growth in production volume. Management is guiding for ~50% gross margin at a $60M annual revenue run-rate.

Valuation: Blended P/S and DCF Values VLRX at ~$12/share
Our assumptions above imply U.S. revenue will grow from $19.6M in 2016 to almost $230M (~2% market share) in 2031. Gross margin expansion and improvement in operating leverage (we model a more marked inflection in operating leverage beginning in 2018) should result in Valeritas reaching a point of cash flow break even by 2022 - 2023 or possibly slightly earlier (for reference PODD burned $12.5M in operating cash on $324M in revenue in 2015). Using these inputs as well as a 10.5% discount rate and 2% terminal growth rate, our 15-year **DCF values VLRX at approximately $12/share**.

We also use Insulet Corp (PODD), manufacturer of the OmniPod System (discussed earlier) as a comp for valuation purposes. PODD trades at approximately 6x and 5x analysts' estimated 2016 and 2017 revenue – which **implies fair value of VLRX of between approximately $10 and $11 per share**. While we acknowledge PODD's much more established position, marketing infrastructure and size ($2.4B market cap), we think these are offset by the company's long history of consistent and significant negative cash flow and earnings, coupled with growth prospects which we think are less attractive than VLRX's. As such, we believe PODD is a fair comparable.

And finally, as a triple-check to reasonableness of our fair value calculation, in 2010 Roche acquired 100% of Medingo Ltd, maker of the Solo insulin patch pump (discussed earlier) for a $160M (with the potential for up to $40M in performance milestones). A $160M market capitalization, would **imply VLRX is worth approximately $12.5/share**.

FINANCIAL MODEL

Valeritas Holdings, Inc. (figures in 000s of $)

Valeritas	2015 A	Q1A	Q2A	Q3A	Q4E	2016 E	2017 E	2018 E	2019 E
U.S. V-Go									
New reps this year		0	0	0	0	0	13	5	2
Total reps		28	28	28	28	28	41	46	48
Blended productivity	**-**	**16.8**	**16.8**	**16.8**	**16.8**	**16.8**	**20.1**	**28.9**	**38.3**
Max TRx/rep	-	1,350	1,350	1,350	1,350	5,400	5,508	5,618	5,731
TRx this period	92,000	22,680	22,680	22,680	22,680	90,720	110,435	162,084	219,479
YOY growth	-	-	-	-	-	*-1.4%*	*21.7%*	*46.8%*	*35.4%*
U.S. V-Go Revenue	**$18,097**	**$5,009**	**$4,884**	**$4,859**	**$4,879**	**$19,631**	**$24,686**	**$37,680**	**$53,319**
YOY growth	-	-	-	-	-	-	*25.7%*	*52.6%*	*41.5%*
Net Price/Unit	$5.32	$5.97	$5.82	$5.79	$5.81	$5.85	$6.04	$6.28	$6.57
YOY growth	-	-	-	-	-	*10.0%*	*3.3%*	*4.0%*	*4.5%*
Initial Tgt Mrkt Size	$11,000,000	$2,750,000	$2,750,000	$2,750,000	$2,750,000	$11,000,000	$11,110,000	$11,221,100	$11,333,311
Market Share	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.3%	0.5%
Total Revenues	$18,097.0	$5,009.0	$4,885.0	$4,860.0	$4,879.4	$19,633.4	$24,685.6	$37,679.8	$53,318.5
YOY Growth	*34.1%*	*20.6%*	*6.2%*	*2.6%*	-	*8.5%*	*25.7%*	*52.6%*	*41.5%*
Cost of Goods Sold	$14,237.0	$3,297.0	$3,160.0	$3,132.0	$3,142.3	$12,731.3	$15,551.9	$22,607.9	$30,391.6
Gross Income	$3,860.0	$1,712.0	$1,725.0	$1,728.0	$1,737.1	$6,902.1	$9,133.7	$15,071.9	$22,927.0
Gross Margin	*21.3%*	*34.2%*	*35.3%*	*35.6%*	*35.6%*	*35.2%*	*37.0%*	*40.0%*	*43.0%*
R&D	$6,523.0	$1,261.0	$1,186.0	$1,188.0	$1,197.0	$4,832.0	$5,455.5	$5,727.3	$5,918.4
% SG&A	*36.0%*	*25.2%*	*24.3%*	*24.4%*	*24.5%*	*24.6%*	*22.1%*	*15.2%*	*11.1%*
SG&A	$44,680.0	$8,409.0	$8,141.0	$7,997.0	$8,130.0	$32,677.0	$37,571.5	$41,334.8	$44,947.5
% R&D	*246.9%*	*167.9%*	*166.7%*	*164.5%*	*166.6%*	*166.4%*	*152.2%*	*109.7%*	*84.3%*
Other	$0.0	$1,762.0	$401.0	$198.0	$440.0	$2,801.0	$604.0	$0.0	$0.0
Operating Income	($47,343.0)	($9,720.0)	($8,003.0)	($7,655.0)	($8,029.9)	($33,407.9)	($34,497.3)	($31,990.2)	($27,938.9)
Operating Margin	*-261.6%*	*-194.1%*	*-163.8%*	*-157.5%*	*-164.6%*	*-170.2%*	*-139.7%*	*-84.9%*	*-52.4%*
Total Other Income (Expense)	($19,852.0)	($7,178.0)	($2,463.0)	($1,502.0)	($1,600.0)	($12,743.0)	($6,400.0)	($6,400.0)	($6,400.0)
Pre-Tax Income	($67,195.0)	($16,898.0)	($10,466.0)	($9,157.0)	($9,629.9)	($46,150.9)	($40,897.3)	($38,390.2)	($34,338.9)
Tax expense (benefit)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Tax Rate	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Net Income	($67,195.0)	($16,898.0)	($10,466.0)	($9,157.0)	($9,629.9)	($46,150.9)	($40,897.3)	($38,390.2)	($34,338.9)
YOY Growth	*-10.3%*	*-31.1%*	*-35.2%*	-	-	*-31.3%*	*-11.4%*	*-6.1%*	*-10.6%*
Net Margin	-	-	-	-	-	-	-	-	*-64.4%*
EPS	($6.14)	($1.48)	($1.09)	($0.72)	($0.76)	($3.98)	($2.21)	($1.63)	($1.23)
YOY Growth	*-67.5%*	-	-	-	-	*-35.1%*	*-44.5%*	*-26.1%*	*-24.9%*
Diluted Shares O/S	10,951	11,410	9,562	12,680	12,700	11,588	18,500	23,500	28,000

Brian Marckx, CFA

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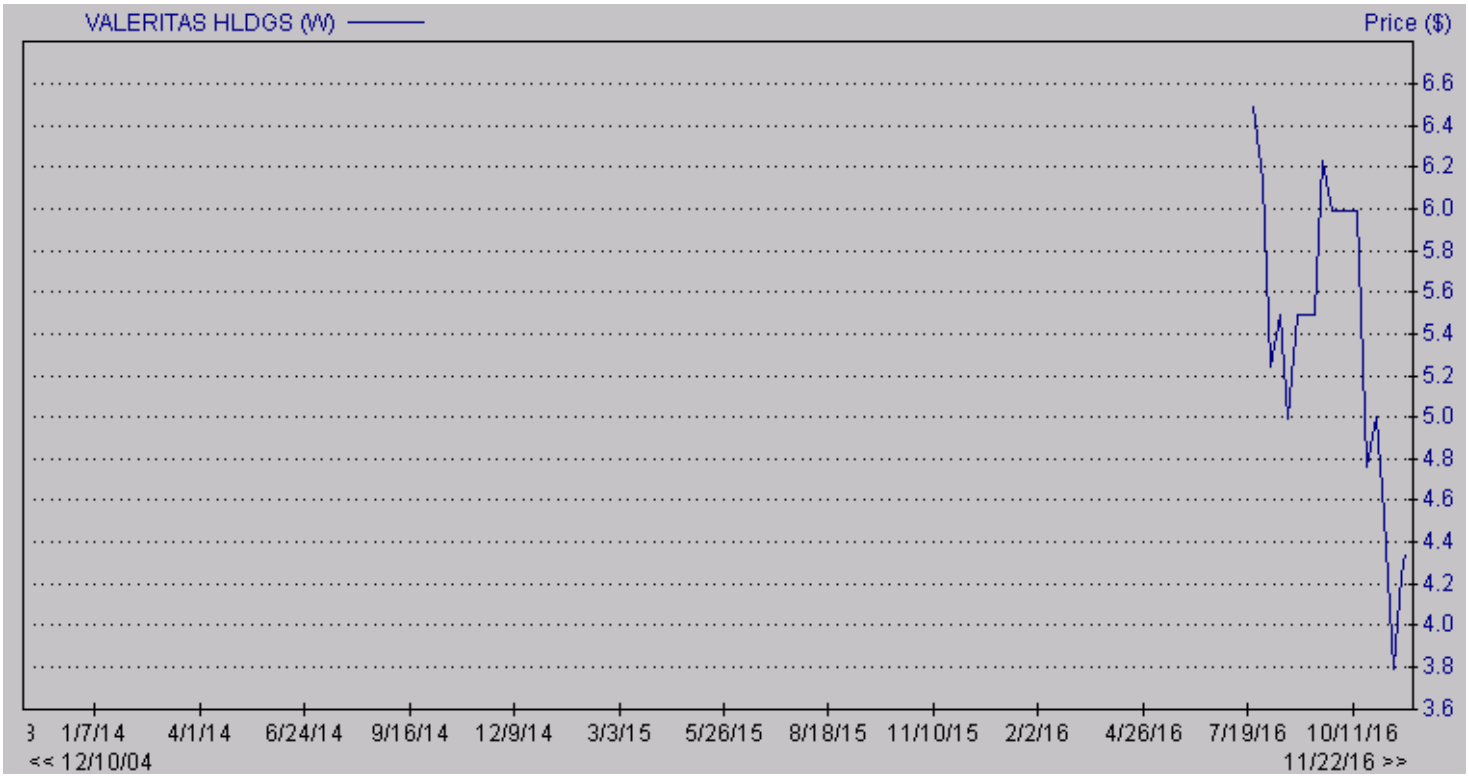
HISTORICAL STOCK PRICE



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