Zacks Small-Cap Research

May 23, 2017

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Valeritas Holdings, Inc. (VLRX- NASDAQ)

VLRX: High-Touch Strategy Showing Early Successes

Based on blended DCF and P/S comp, we value VLRX at $19/share. Our 15-year DCF, which uses a 10.5% discount rate and 2% terminal growth rate values VLRX at $18/share. P/S using PODD as comp values VLRX at $18 - $20/share.

Current Price (05/23/17)	$4.99
Valuation	**$19.00**

OUTLOOK

Given the novel nature of V-Go, it may be that it takes a more in-depth and comprehensive amount of hand-holding at the physician-office level to spark adoption. This may already be taking hold, however. Many of the current highest prescribing accounts are those that have had exposure to the higher-touch servicing approach. And while the lack of revenue growth in Q1 may not necessarily suggest traction in either adoption or prescription growth, other metrics, which management shared on the call, might. Specifically, VLRX noted that the eight territories which were detailed with the same sales reps throughout 2016 and through Q1 2017 (i.e. "stable accounts") saw a 6% increase in revenue from 1H 2016 to 2H 2016. As a reminder, VLRX began implementation of their new sales strategy around mid-2016, which cut the number of accounts that each rep was responsible for calling on from 60 down to 30 ("targeted accounts"). Average revenue growth of these targeted accounts (i.e. targeted with the new high-touch sales model) was even stronger – up 10% from 1H 2016 to 2H 2016.

SUMMARY DATA

52-Week High	**$52.00**
52-Week Low	**$4.51**
One-Year Return (%)	**N/A**
Beta	**N/A**
Average Daily Volume (sh)	**40,479**
Shares Outstanding (mil)	**7**
Market Capitalization ($mil)	**$34**
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 2017 Estimate	**N/A**
P/E using 2018 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**High,**
Type of Stock	**N/A**
Industry	**Med Products**

ZACKS ESTIMATES

Revenue
(in 000s of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2016	5009 A	4885 A	4860 A	4796 A	19,550 A
2017	4611 A	5142 E	5698 E	6388 E	21,839 E
2018					28,101 E
2019					38,473 E

Earnings per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2016	-$47.33 A	-$8.76 A	-$5.78 A	-$6.19 A	-$39.2 A
2017	-$6.95 A	-$1.53 E	-$1.53 E	-$1.48 E	-$7.69 E
2018					-$6.09 E
2019					-$3.49 E

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

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WHAT'S NEW…

Q1 Results / High-Touch Strategy Showing Early Successes, Expect Sequential Growth Throughout 2017:

Valeritas reported Q1 financial results and provided a business update. Relative to our estimates, revenue was almost dead-on, gross margin meaningfully wider (and what looks to be an historic best) and operating expenses higher.

Revenue, at $4.61M, was down 8% yoy, 4% lower than Q4 2016 and inline with our $4.63M estimate. The yoy revenue contraction was attributed to a decline in the size of the sales force as well as weakness in the overall insulin market.

Specifically, the sales force in Q1 2017 averaged 34 reps, or 15% less than the 40 averaged in Q1 2016 as VLRX vacated low performing territories and consolidated resources around higher prescribing accounts with their high-touch sales and servicing strategy. While the vacated accounts were largely inefficient to service, their attrition nonetheless resulted in a ~10% decrease in total V-Go prescriptions – that was partially offset by a 2.4% net increase in average pricing. Relative to the U.S. insulin market, management noted on the call that total prescriptions fell 9% in January and 15% in February 2017 as compared to the same periods in 2016.

Gross margin, at 37.6%, was certainly a highlight and up from 34.2% and 37.2% in Q1 and Q4 of last year, respectively. This is also the widest GM among VLRX publicly available financials. Management has consistently noted that they expect GM to continue to improve as a result of manufacturing efficiencies and other expense containment measures and those activities appear to be bearing fruit. While GM will contract in Q3 this year as a result of inventory burn-through (carried at a higher cost), that incremental expense should be non-cash. VLRX continues to guide for gross margin to also benefit from higher production volumes as revenue accelerates and expects GM in Q4 to best that of the comparable prior year period (which was a relatively beefy 37.1%). Longer-term, management believes they can now achieve 50% GM at a quarterly revenue level of approximately $13M.

Meanwhile **operating expenses** moved up to $12.0M in Q1, compared to $9.7M and $10.1M in Q1 and Q4 2016, respectively. An increase in stock-based compensation in the amounts of ~$840k (vs Q1 2016) and ~$970k (vs Q4 2016) accounts for much of the relative increase. We model OpEx to remain flattish to Q1 through the remainder of 2017 as incremental expense related to additions to the sales force are offset by expectations of comparably lower stock compensation. However, control over operating expenses will be key to improving profitability going forward – which in-turn will largely hinge of the efficiency and productivity (i.e. revenue per rep) of the sales force.

As it relates to that, early indications are that the newly implemented high-touch sales process may be resulting in greatly improved productivity – with management noting on the call that many of their highest prescribing accounts were those with more sales rep visits and serviced with a more 'hand-holding' (our word) type approach. As such, and assuming further roll-out of the high-touch and higher service strategy continues to result in an overall improvement in productivity, growth in revenue should outpace that of operating expenses.

Cash

Cash used in operating activities in Q1 was $8.0M ($8.5M ex-changes in working capital), compared to $10.9M ($7.4M ex-changes in working capital) in Q1 2016 and $5.7M ($7.0M ex-changes in working capital) in Q4 2016. Cash balance, bolstered by the $48.8 (net) equity raise in March, was $51.8M at Q1 quarter-end. At the current burn rate (~$8M/qtr), this represents approximately 19 months (or through ~October 2018) worth of operating capital.

The equity raise not only provided a substantial operating runway, it also substantially relaxed the debt burden. Concurrent with the equity raise, VLRX converted 50% of the total $55M in (then) outstanding debt into preferred stock. And while the debt-to-preferred conversion does not have an immediate significant positive impact on reducing cash-related debt servicing (given that the debt interest was PIK), amendments extending by one year the final maturity as well when cash interest payments begin on the remaining debt balance **provided additional flexibility and liquidity down the road**. Additionally, the minimum cash balance covenant was reduced from $5M to $2M.

Weeding Underperforming Accounts, High-Touch Strategy Aimed at Accelerating Adoption
VLRX slashed the direct sales force from 64 in January 2016 to 37 as of the start of 2017 – the massive headcount reduction followed the decision to abandon underperforming accounts that were inefficient to service. The relatively few prescriptions written from these offices were not worth the cost and effort to target. Instead VLRX refocused with a higher-touch sales strategy on higher potential prescribers. This higher-touch approach, as described by management, is more fully-encompassing as it relates to facilitating adoption of V-Go. This includes educating not only the prescribing physicians on the benefits and use of V-Go but also addressing responsibilities of other patient-centric personnel, such as help in navigating any reimbursement-related nuances.

Given the novel nature of V-Go, it may be that it takes a more in-depth and comprehensive amount of hand-holding at the physician-office level to spark adoption. This may already be taking hold, however. As noted, many of the current highest prescribing accounts are those that have had exposure to the higher-touch servicing approach. And while the lack of revenue growth may not necessarily suggest traction in either adoption or prescription growth, other metrics, which management shared on the Q1 call, might.

Specifically, VLRX noted that the eight territories which were detailed with the same sales reps throughout 2016 and through Q1 2017 (i.e. "stable accounts") saw a 6% increase in revenue from 1H 2016 to 2H 2016. As a reminder, VLRX began implementation of their new sales strategy around mid-2016, which cut the number of accounts that each rep was responsible for calling on from 60 down to 30 ("targeted accounts"). Average revenue growth of these targeted accounts (i.e. targeted with the new high-touch sales model) was even stronger – up 10% from 1H 2016 to 2H 2016.

These metrics also certainly seem to support that the high-touch approach is resulting in revenue growth and, by extension, prescription growth and likely higher rates of adoption. And, importantly, these "same-territory sales" are also a measure of efficiency and production as intuitively it should be less costly to service those accounts where the in-depth (mostly initial) hand-holding is no longer necessary. As such, we think these metrics provide important insight into fundamental operational performance, particularly during the transition from a more shotgun sales approach with each rep detailing to a large number of accounts, to a strategy focused on a more select number of high potential prescribers.

Q2 will be the first full quarter with the new sales strategy in place. And with 48 reps on-board at the start of the quarter (with expectations this will average ~45), compared to an average of 34 throughout Q1 2017, we expect sequential revenue growth throughout 2017 with greater acceleration in the back half of the year. Productivity gains from new reps should be the low-hanging fruit in terms of driving near-term revenue growth. Longer-term, the ability of the sales force to successfully convey the clinical and lifestyle benefits of V-Go as compared to MDI will be key. The high-touch approach appears to be bearing fruit in that regard, although the next few quarters should provide even greater insight.

International Expansion Could Offer Complementary Revenue Opportunity…
Along with being FDA-cleared, V-Go is also CE Marked, allowing it to also be sold in Europe as well as other territories that recognize that designation of regulatory and marketing approval. While VLRX has spoken only relatively sparsely about potential international expansion, we think it remains on their radar. If and when that happens, we expect it would be via distribution agreements which, while likely not quite as profitable at the margin as compared to direct sales, all but eliminates any downside risk and could afford relatively rapid and broad geographic coverage in parts of Europe. This will be something we hope to hear updates about in the future, particularly as **international expansion could provide upside to our current model**.

Clinical Data Continues To Support Health Benefits of V-Go vs. Pens/Needles
Valeritas remains very active in adding to their clinical evidence database supporting the clinical and economic benefits of V-Go, particularly as compared to traditional insulin delivery methods. **Clinical evidence continues to show V-Go more effectively controls A1C than insulin pens/needles and does so with lower insulin doses and associated cost.**

The benefits of V-Go were on display during two clinical data-related presentations at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) annual meeting yesterday (May 23rd). One study showed that among 86 patients who had difficulty controlling A1C and switched from MDI to V-Go, average A1C levels fell by 1.2%, daily insulin dose fell 44% and average monthly costs fell by $146.

The other study compared treatment outcomes and costs between study sites using V-Go versus those using other type 2 diabetes therapies. Results showed that the V-Go study sites had a larger decrease in average A1C (-1.015% vs. -0.377%) and lower average per patient cost ($30.59 vs. $32.60).

Relative to recent publications, data from a retrospective study comparing V-Go to traditional insulin delivery in nursing home patients was published in the January 2017 issue of the Journal of Gerontological Nursing. The study, which included 1,937 blood glucose levels of eight nursing home patients collected over 61 days showed V-Go was not only associated with highly statistically significant superior blood glucose lowering efficacy and control as compared with needles/pens, it also reduced the time consumed by nursing home staff to administer insulin and lowered the related cost (as compared to traditional insulin delivery).

Specifically, V-Go patients exhibited significant improvements in the amount of time that A1C remained in the recommended range (V-Go 59.1% vs. traditional 34.0%, $p<0.001$), reduced blood glucose fluctuations ($p<0.001$) and improved mean daily blood glucose ($p<0.001$). In addition, estimated A1C change among the V-Go cohort fell from 8.9% to 7.2% while the traditional insulin cohort exhibited an increase from 9.0% to 9.4%. Relative to staff time and cost, V-Go decreased the average amount of staff time required for insulin administration by 26 minutes per patient per day and related labor cost by almost $329 per patient per month[1].

[1] Boonin A, Balinski B, Sauter J, Martinez J, Abbott S. A Retrospective Chart Review of Two Different Insulin Administration Systems on Glycemic Control in Older Adults in Long-Term Care. J Gerontol Nurs. 2017 Jan 1;43(1):10-16. doi: 10.3928/00989134-20161215-04.

BACKGROUND

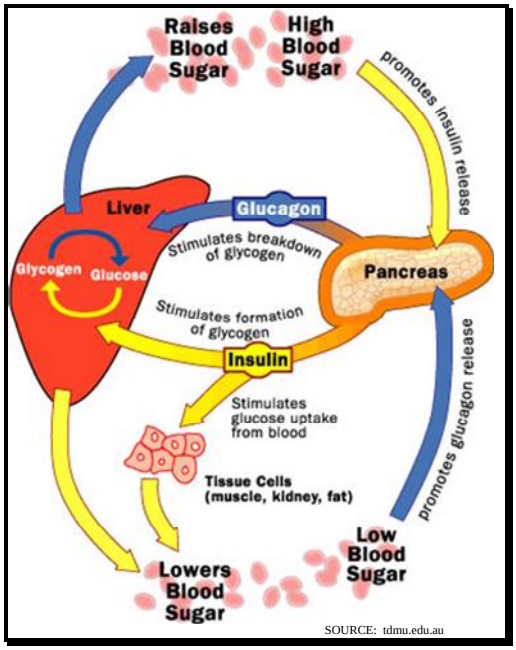
Insulin

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.

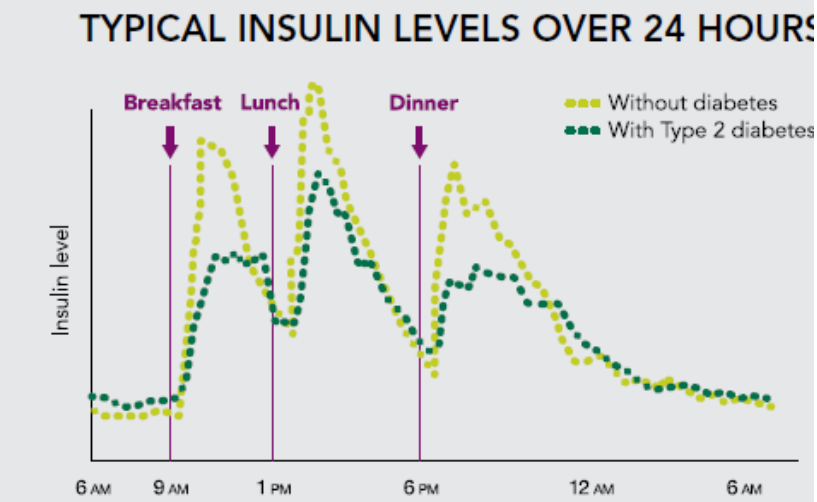
While many individuals with type 1 diabetes experience a 'honeymoon period' shortly following initial insulin therapy whereby the pancreas is able to produce some insulin, this is typically short-lived as the ability to produce insulin quickly deteriorates. Unlike type 2 diabetics, which oftentimes can 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;

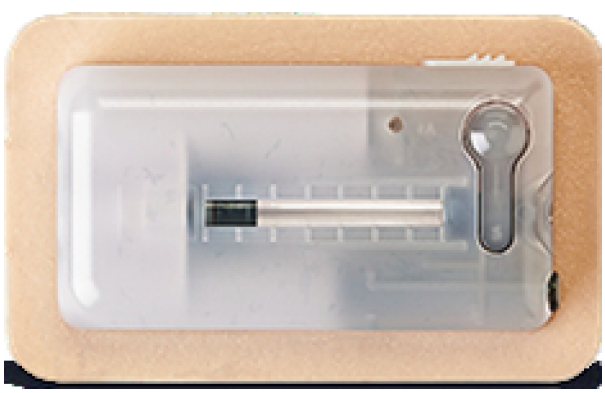
- FPG = 100 - 125 mg/dl (5.6 - 6.9 mmol/L), defined as 'impaired fasting glucose' (IFG)
- 2-hour PG = 140 - 199 mg/dl (7.8 - 11.0 mmol/L), defined as 'impaired glucose tolerance' (IGT)
- A1C = 5.7% - 6.4% (39 - 46 mmol/mol)

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



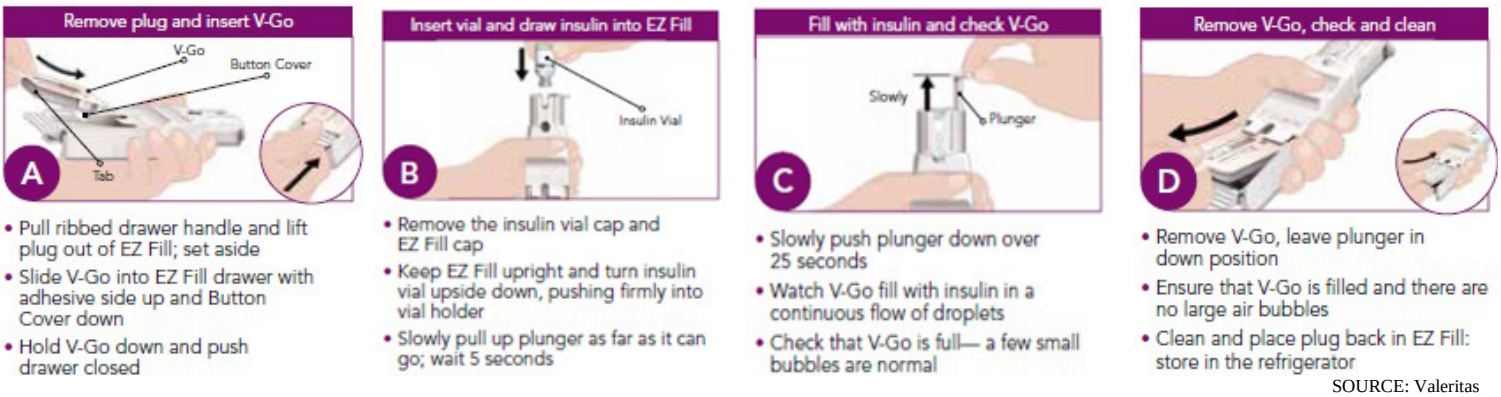


SOURCE: Valeritas

Operating Instructions: "Fill, Wear and Go"…

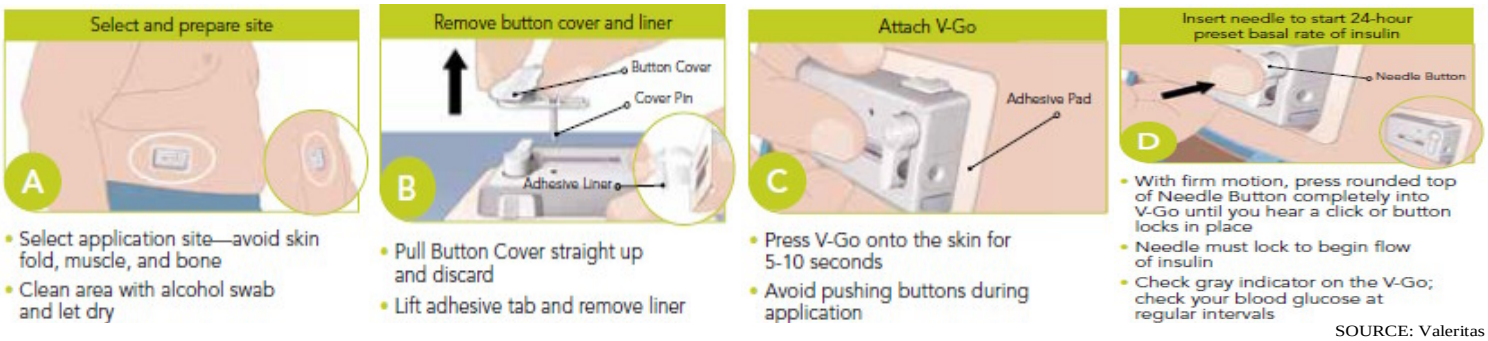
V-Go was specifically designed for simple and easy administration and to eliminate as much of the physical and mental burden of insulin therapy as possible. By doing so V-Go addresses most of the psychological issues related to initial adoption of insulin therapy among insulin naïve (i.e. psychological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

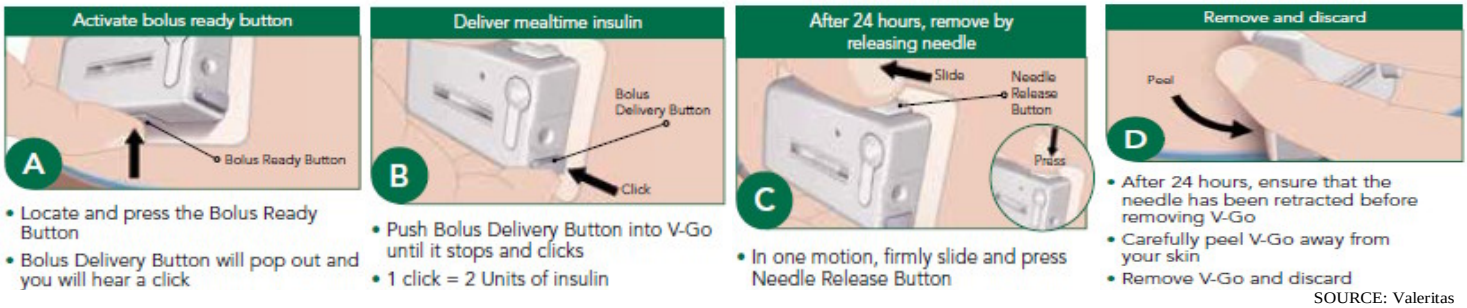
2) Wear: After V-Go is filled with insulin, the user removes a liner to expose an adhesive strip, places the cartridge on a flat part of the stomach or back of the arm and inserts the needle with a button push which also starts the flow of insulin. (See below for description of the insulin delivery technology).



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 has noted 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.

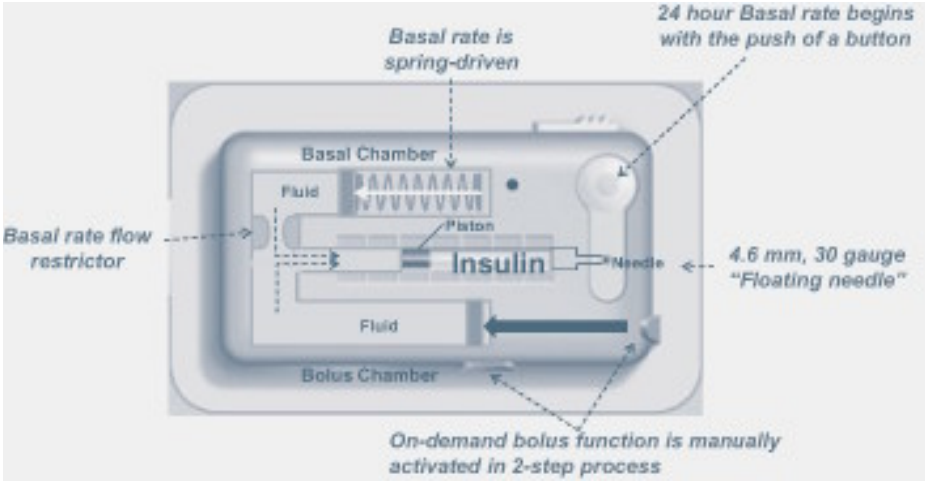
V-Go option	Preset basal rate	+	On-demand bolus dosing	=	Total available insulin
VGO 20 DISPOSABLE INSULIN DELIVERY	20 Units/24 hr (0.83 U/hr)	+	Up to 36 Units in 2-Unit increments*	=	56 Units
VGO 30 DISPOSABLE INSULIN DELIVERY	30 Units/24 hr (1.25 U/hr)	+	Up to 36 Units in 2-Unit increments*	=	66 Units
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 21 U.S. and 56 international issued patents and 8 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' public filings 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 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

[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

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

[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.

lag between the optimal point that a particularly patient should begin insulin therapy and when it actually 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.

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[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.

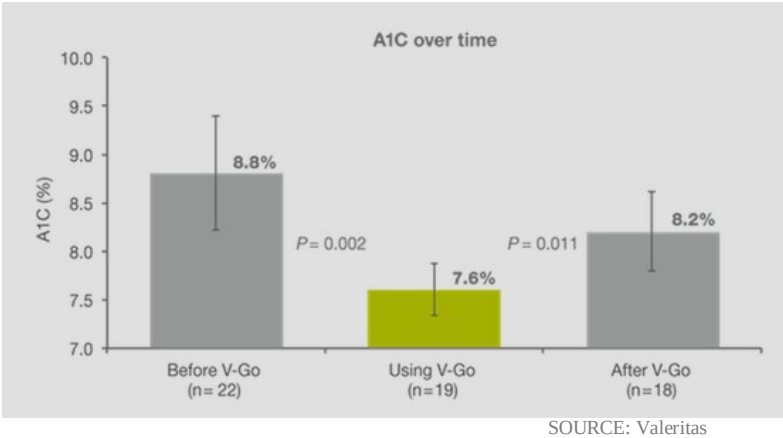
On all parameters average score ranged between 8.7 and 9.4. We think particularly noteworthy is that 'ease of use' and 'discreet', which studies have indicated are major factors for psychological insulin resistance, both averaged 9.3 (i.e. high) in this UPP study. Adherence to V-Go was also surveyed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

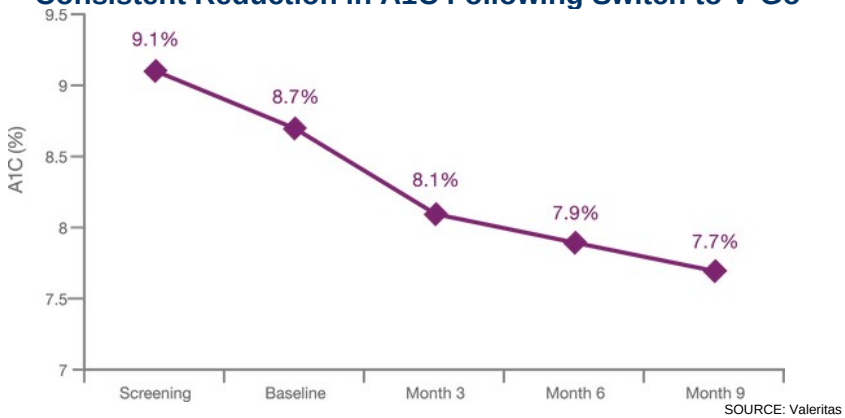
[20] Odegard PS, Gray SL. Barriers to medication adherence in poorly controlled diabetes mellitus. Diabetes Educ. 2008;34:692–697.



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

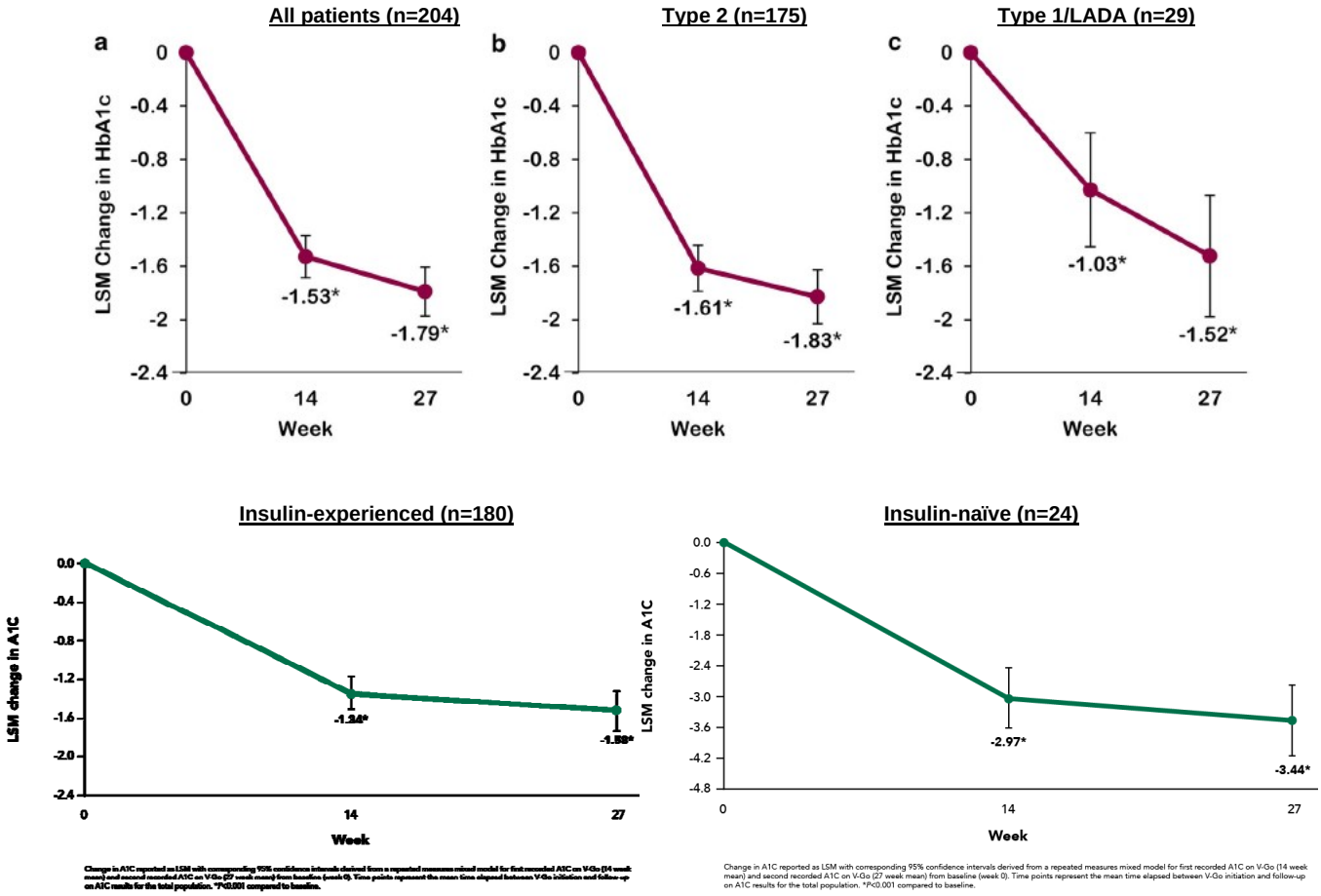


SOURCE: Valeritas

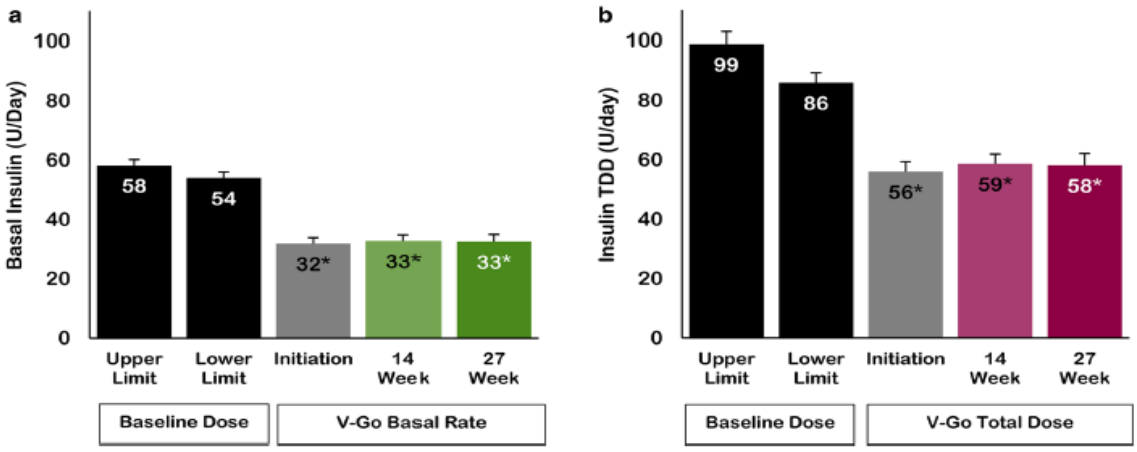
- **Diabetes America Study:** showed statistically significant reductions in A1C and insulin usage when patients switched from injections to V-Go. Retrospective analysis of 204 type 1 (and LADA) (n=29) and type 2 diabetes (n=175) patients which were either prescribed basal-bolus insulin therapy (n=180) 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

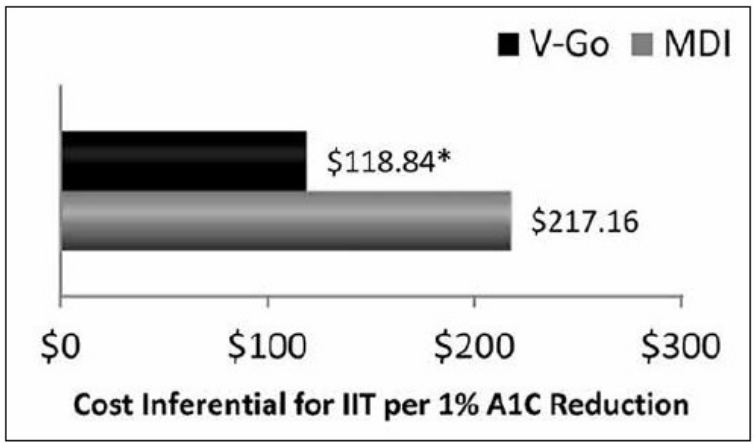


Statistically Significant Reductions in Insulin Usage When Switched to V-Go



- **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)

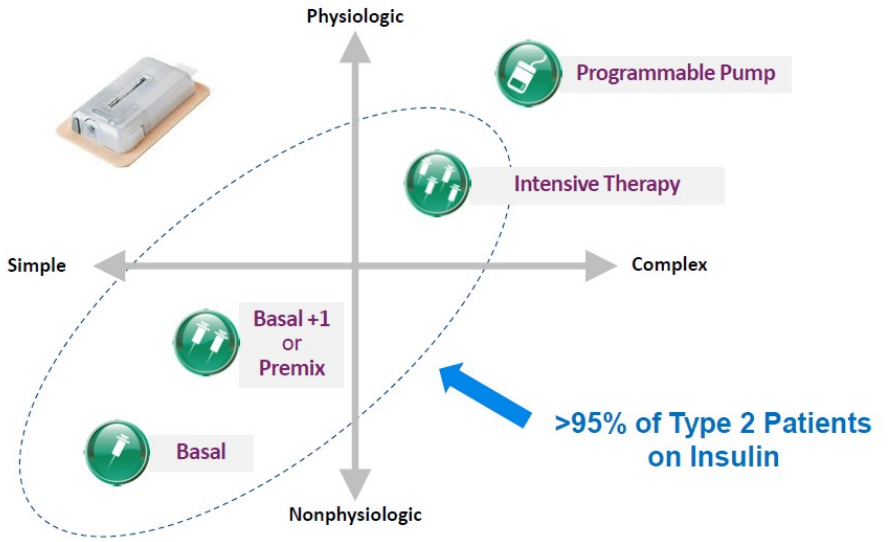
- **Results of Other, Smaller Studies Also Support Benefits of V-Go:** other, smaller studies have also been conducted showing similar benefits of improved A1C reduction and lower insulin use with V-Go. These include;
    - **Early Access Program (n=16):** after three months of V-Go therapy, patients' 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.
    - **Retrospective Nursing Home Study:** data from a retrospective study comparing V-Go to traditional insulin delivery in nursing home patients was published in the January 2017 issue of the Journal of Gerontological Nursing. The study, which included 1,937 blood glucose levels of eight nursing home patients collected over 61 days showed V-Go patients exhibited significant improvements in the amount of time that A1C remained in the recommended range (V-Go 59.1% vs. traditional insulin delivery 34.0%, $p<0.001$), reduced blood glucose fluctuations ($p<0.001$) and improved mean daily blood glucose ($p<0.001$). In addition, estimated A1C change among the V-Go cohort fell from 8.9% to 7.2% while the traditional insulin cohort exhibited an increase from 9.0% to 9.4%. Relative to staff time and cost, V-Go decreased the average amount of staff time required for insulin administration by 26 minutes per patient per day and related labor cost by almost $329 per patient per month .

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 the U.S. in 1H 2017.
- **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

Valuation: Blended P/S and DCF Values VLRX at ~$19/share

Our assumptions imply U.S. revenue will grow from $19.6M in 2016 to approximately $175M (< 2% market share) in 2031. Gross margin expansion and improvement in operating leverage (we model inflection in operating leverage beginning in 2H 2018) should result in Valeritas reaching a point of cash flow break even by 2023 - 2024 or possibly slightly earlier (for reference PODD generated $15.9M in operating cash on $367M in revenue in 2016). Using these inputs as well as a 10.5% discount rate and 2% terminal growth rate, our 15-year DCF values VLRX at approximately $18/share.

We also use Insulet Corp (PODD), manufacturer of the OmniPod System (discussed earlier) as a comp for valuation purposes. PODD trades at approximately 5.7x and 5.0x analysts' estimated 2017 and 2018 revenue – which implies fair value of VLRX of between approximately $18 and $22 per share. While we acknowledge PODD's much more established position, marketing infrastructure and size ($2.5B market cap), we think these are offset by the company's long history of consistent and significantly negative earnings as well as 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 $23/share.

FINANCIAL MODEL

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

Valeritas	2016 A	Q1A	Q2E	Q3E	Q4E	2017 E	2018 E	2019 E	2020 E
Total Revenues	$19,550.0	$4,611.0	$5,141.8	$5,698.2	$6,387.7	$21,838.6	$28,100.8	$38,473.2	$51,385.1
YOY Growth	*8.0%*	*-7.9%*	*5.3%*	*17.2%*	*33.2%*	*11.7%*	*28.7%*	*36.9%*	*33.6%*
Cost of Goods Sold	$12,606.0	$2,878.0	$3,229.0	$3,886.2	$4,005.1	$13,998.3	$17,141.5	$21,929.7	$26,514.7
Gross Income	$6,944.0	$1,733.0	$1,912.7	$1,812.0	$2,382.6	$7,840.4	$10,959.3	$16,543.5	$24,870.4
Gross Margin	*35.5%*	*37.6%*	*37.2%*	*31.8%*	*37.3%*	*35.9%*	*39.0%*	*43.0%*	*48.4%*
R&D	$4,842.0	$1,588.0	$1,461.0	$1,442.0	$1,529.0	$6,020.0	$5,086.2	$5,309.3	$4,933.0
%SG&A	*24.8%*	*34.4%*	*28.4%*	*25.3%*	*23.9%*	*27.6%*	*18.1%*	*13.8%*	*9.6%*
SG&A	$33,481.0	$10,447.0	$9,641.0	$9,715.0	$9,881.0	$39,684.0	$43,949.6	$46,629.5	$50,563.0
%R&D	*171.3%*	*226.6%*	*187.5%*	*170.5%*	*154.7%*	*181.7%*	*156.4%*	*121.2%*	*98.4%*
Other	$2,394.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Operating Income	($33,773.0)	($10,302.0)	($9,189.3)	($9,345.0)	($9,027.4)	($37,863.6)	($38,076.5)	($35,395.4)	($30,625.5)
Operating Margin	*-172.8%*	*-223.4%*	*-178.7%*	*-164.0%*	*-141.3%*	*-173.4%*	*-135.5%*	*-92.0%*	*-59.6%*
Total Other Income (Expense)	($12,594.0)	($1,504.0)	($792.0)	($779.0)	($767.0)	($3,842.0)	($3,211.0)	($3,210.0)	($3,210.0)
Pre-Tax Income	($46,367.0)	($11,806.0)	($9,981.3)	($10,124.0)	($9,794.4)	($41,705.6)	($41,287.5)	($38,605.4)	($33,835.5)
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%*
Preferred dividends	$0.0	$48.0	$550.0	$550.0	$550.0	$1,698.0	$2,200.0	$2,200.0	$2,200.0
Net Income	($46,367.0)	($11,854.0)	($10,531.3)	($10,674.0)	($10,344.4)	($43,403.6)	($43,487.5)	($40,805.4)	($36,035.5)
YOY Growth	*-31.0%*	*-*	*-*	*-*	*-*	*-6.4%*	*0.2%*	*-6.2%*	*-11.7%*
Net Margin	*-*	*-*	*-*	*-*	*-*	*-*	*-*	*-106.1%*	*-70.1%*
EPS	($39.23)	($6.95)	($1.53)	($1.53)	($1.48)	($7.69)	($6.09)	($3.49)	($2.86)
YOY Growth	*-20.1%*	*-*	*-*	*-*	*-*	*-80.4%*	*-20.8%*	*-42.7%*	*-18.0%*
Diluted Shares O/S	1,182	1,706	6,892	6,955	7,010	5,641	7,140	11,700	12,600

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