



An introduction to
VNS THERAPY in depression

The Reality of Difficult to Treat Depression



High Healthcare burden

High healthcare burden ⁽¹⁾

Increased suicide risk ⁽³⁾

High health care utilisation ⁽⁴⁾

Resistant depression accounts for **40%** of annual depression treatment costs ⁽²⁾

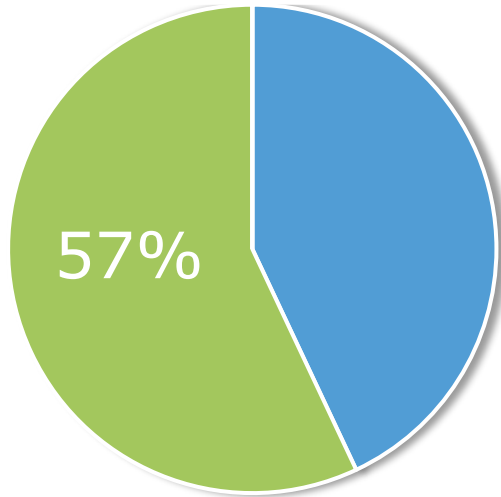


Current Therapy Limited

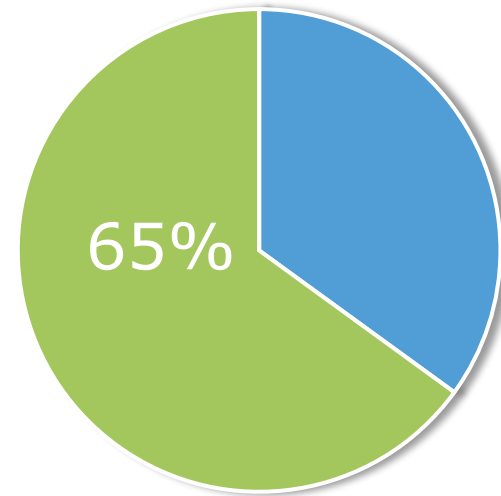
Current antidepressant therapies have limited effectiveness for patients with **true resistant depression** ⁽³⁾

1. Mrazek et al. *Psychiatric Services*, 2014. 2. Keitner et al., *Psychiatr Clin N Am*, 2012
3. Dunner et al., *Journal of Clinical Psychiatry*, 2006. 4. Russell et al., *Journal of Clinical Psychiatry*, 2004.

Challenges of Difficult to Treat Depression



Relapse
during psychopharmaceutical
therapy ⁽¹⁾



Relapse
after remission with ECT
within 6 months ⁽²⁾

1. Zajecka et al., *J Clin Psychiatry*, 2000.

2. Prudic et al., *Biol Psychiatry*, 2004

Treatment of Difficult to Treat Depression

**Aim for long-term
disease management**

Reduce relapse and recurrence

Restore psychosocial function

Reduce risk of suicide

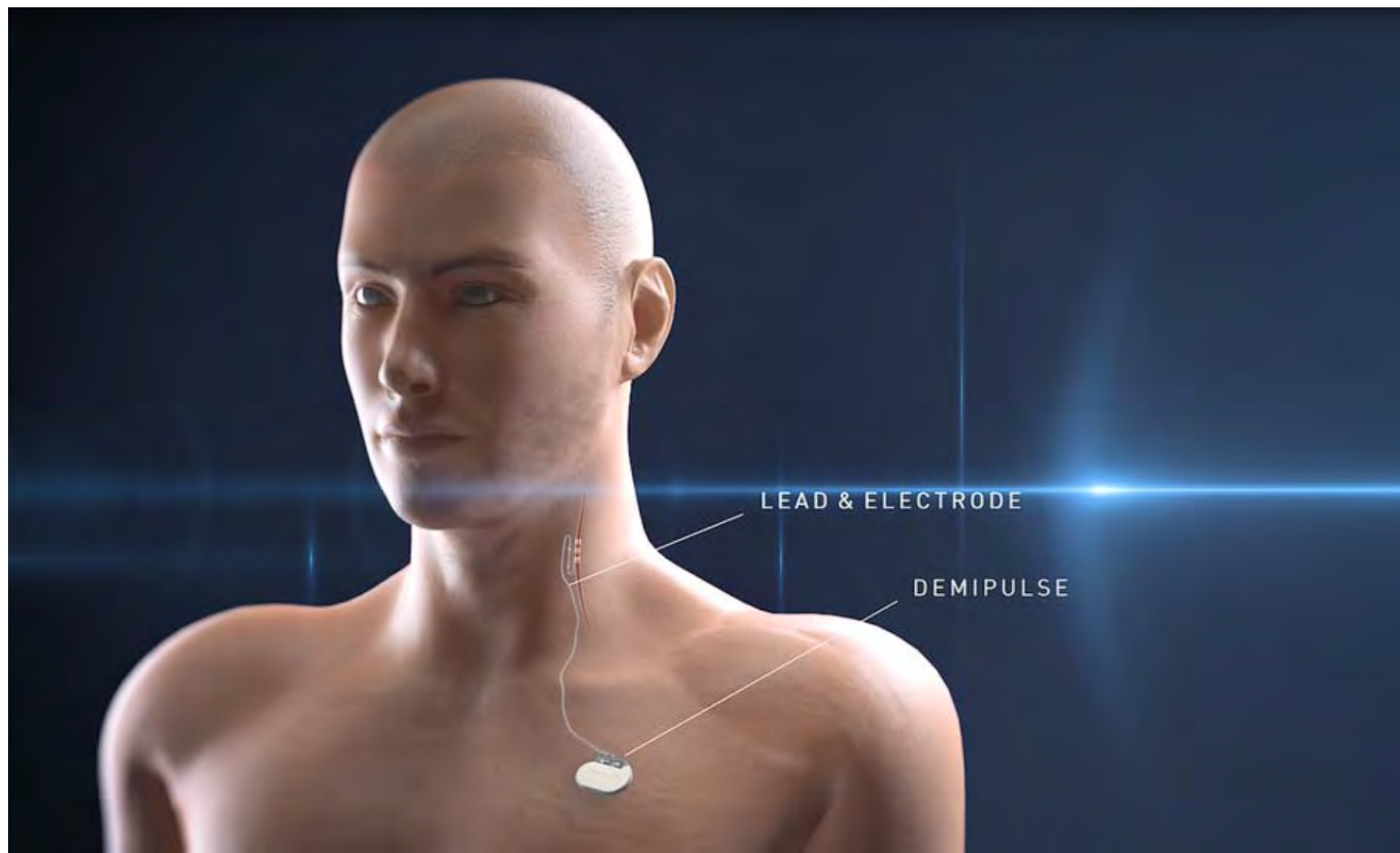
Optimise safety and side-effects

Optimise compliance

Improve Quality of Life⁽²⁾

1. Zajecka et al., J Clin Psychiatry. 2000
2. Bech et al Annals of General Psychiatry 2006, 5(Suppl 1):S17

What is VNS Therapy?



Antidepressant Mechanisms of VNS

Summary



Short- and medium-term antidepressant effects of VNS

Increases availability of serotonin and noradrenalin (1,2)



Emerging antidepressant effects of VNS

May reduce inflammation contributing to depression (4)



Long-term antidepressant effects of VNS

Attenuates interhemispheric imbalance associated with depression (right side inhibition & left side activation) (3)

1. Roosevelt et al 2006 2. Hammond et al 1992 3. Conway et al 2013; 4. Corcoran et al Neuroimmunomodulation. 2005;

History and Study Design

Objective

Follow clinical course and outcome for TRD patients treated with and without adjunctive VNS Therapy (requirement of FDA for approval)

5 Years

Observational study of unipolar or bipolar depression.

500 VNS + TAU 'v' 300 TAU

Treated at same medical centres

Patient
Choice

Subjects permitted to choose between VNS and TAU at screening

D-21

Pts from completed D-21 dose finding study could enter TRD registry

All received VNS and entered the VNS Group

Patient Demographics – Safety Population

Characteristic	VNS Therapy + TAU D23 + D21		TAU
Patient Number	494		301
Female %	70.9		70.1
% Caucasian	96.8		91.0
Mean Age at BL (yrs) (SD)	48.9 (10.1)		49.9 (11.1)
Mean Age at onset of Depression (SD)	20.9 (11.8)		21.1 (11.4)
Mean Age at dx of Depression (SD)	28.9 (10.8)		29.5 (11.9)
# MDE's (mean, SD)	14.9 (24.1)		12.0 (23.9)
# Failed treatments (mean, SD) ¹	8.2 (3.30)		7.3 (2.92)
#Suicide attempts (mean, SD)	1.8 (4.0)		1.2 (2.4)
Prior ECT (%)	57%	★	40%
Psychiatric hospitalisations within 5 years prior to enrollment	3.0 (4.6)	★	1.9 (4.7)
Baseline MADRS Score	33.1 (7.0)	★	29.4 (6.9)

Aaronson et al. American Journal of Psychiatry 2017

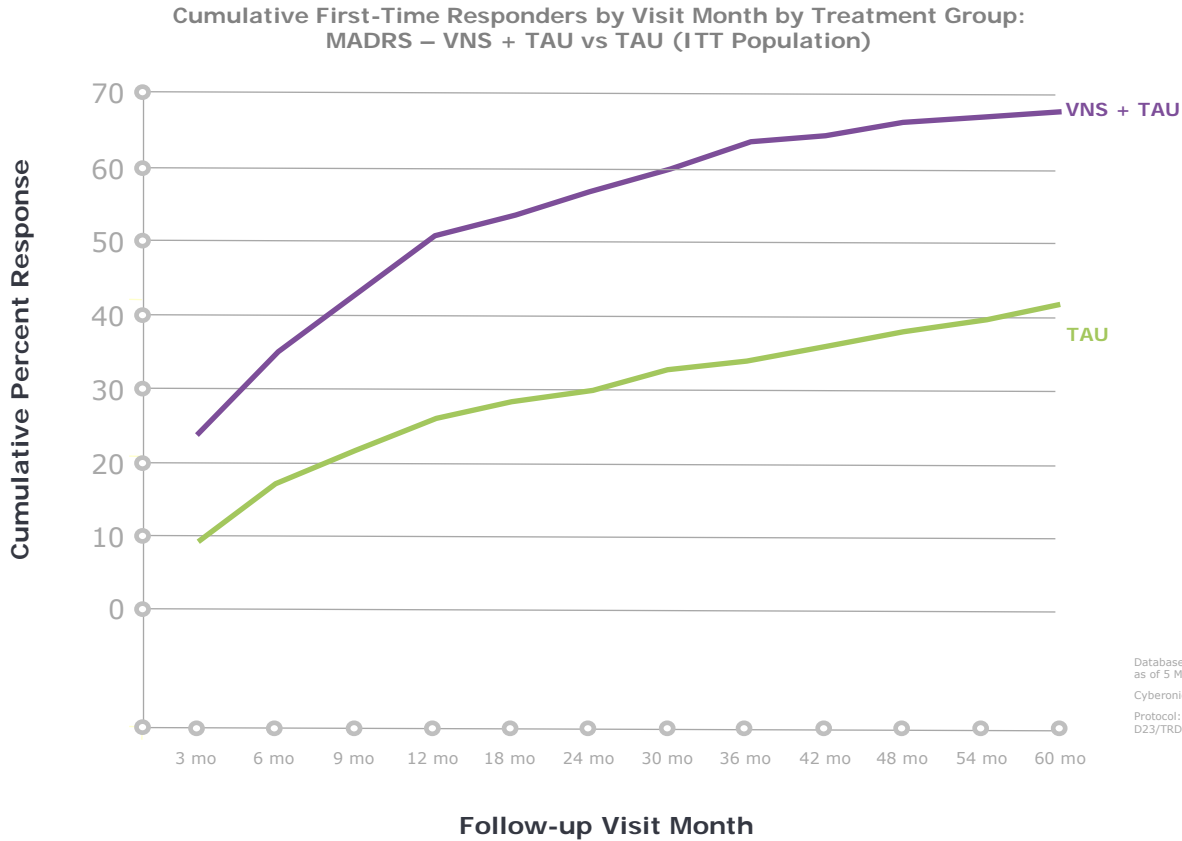
D-23 VNS Registry - US

Patient Demographics

Diagnosis	VNS Therapy + TAU D23 + D21	TAU
Recurrent MDD (moderate)	12.8%	22.9%
Recurrent MDD (severe)	45.5%	31.6%
Single MDD (moderate)	3.2%	10.0%
Single MDD (Severe)	11.3%	12.0%
Bipolar I Depressed (Moderate)	5.1%	7.0%
Bipolar I Depressed (Severe)	12.6%	4.0%
Bipolar II Depressed	9.5%	12.6%

Aaronson et al. American Journal of Psychiatry 2017

Primary Endpoint – First Time **Response Rate** based on MADRS

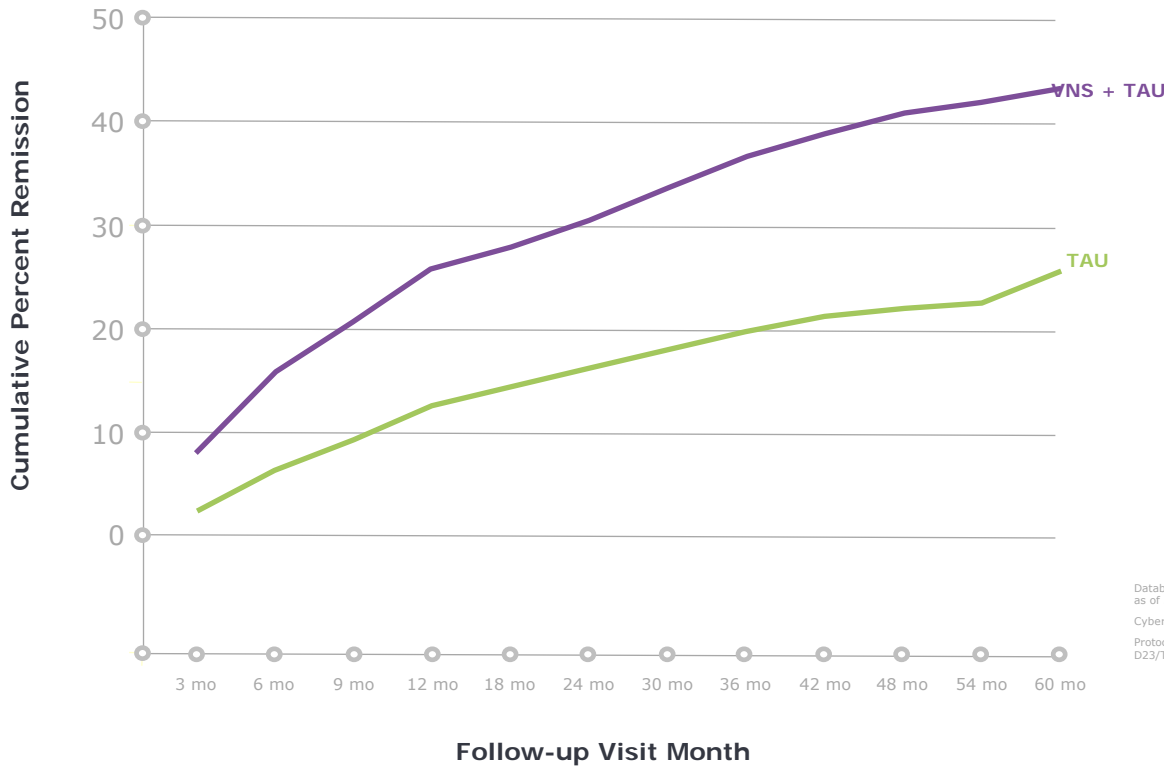


Cumulative Response Rate at 5 years

67.6% for VNS Therapy vs. 40.9% for TAU (P<0.001)

Secondary Endpoint – First Time **Remission Rate** based on MADRS (≤ 9)

Cumulative First-Time Remitters by Visit Month by Treatment Group:
MADRS – VNS + TAU vs TAU (ITT Population)



**Cumulative
Remission Rate
at 5 years**

43.3% for VNS Therapy
D-23 + D-21 vs. 25.7%
for TAU (P<0.001)

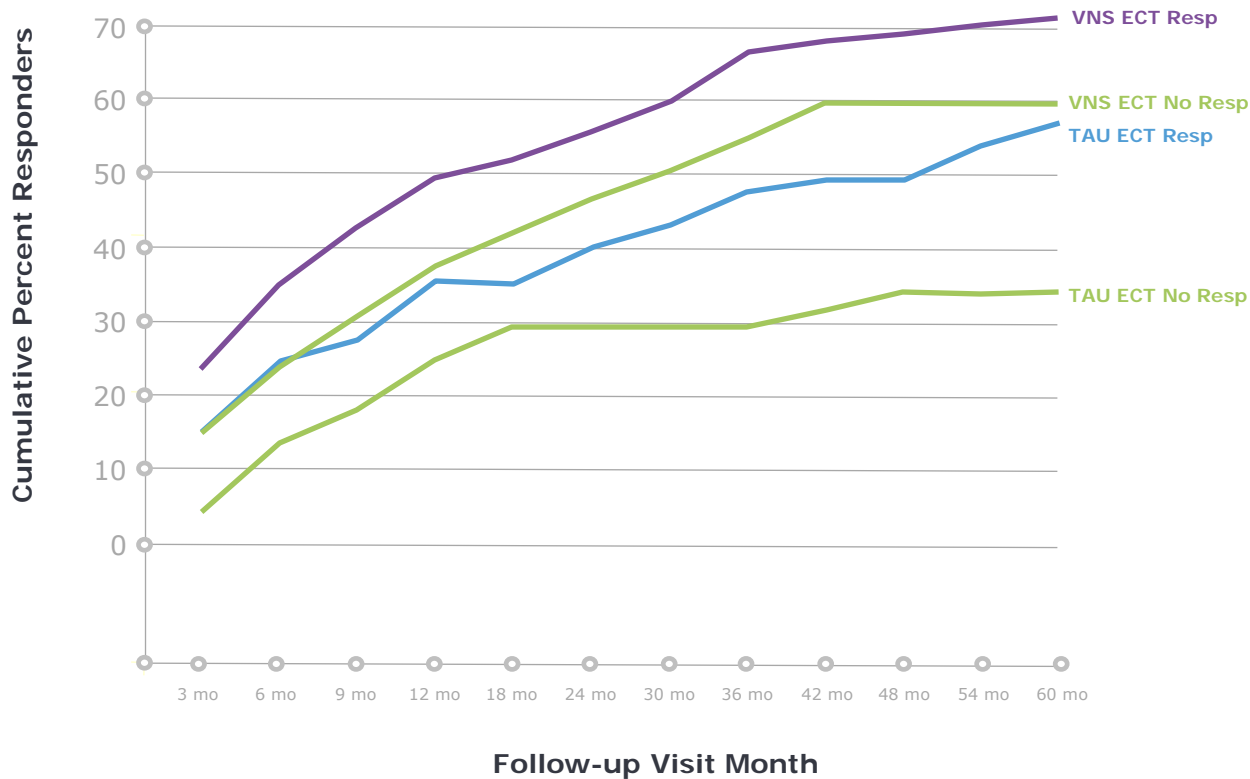
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as of 5 May, 2015
Cyberonics Inc.
Protocol:
D23/TRD Registry

D-23 VNS Registry - US

MADRS – Response by History of Prior Response to ECT

Exploratory Analysis – **Response** based on MADRS

Cumulative First-Time Response by Visit Month by Treatment Group:
MADRS – VNS D-23 + D-21 vs. TAU (ITT Population) based on whether
subjects had responded or not to ECT



Cumulative Response Rate Based on ECT Response (yes/no)

VNS (ECT resp)	(n=129)	71.3%
TAU (ECT resp)	(n=37)	56.9%
VNS (ECT nonresp)	(n=65)	59.7%
TAU (ECT nonresp)	(n=15)	34.0%

VNS for Depression in England – Current Spread of Centres



Conclusions

VNS Therapy® is an **effective treatment** for Difficult to Treat Depression

There is a **significant cumulative and sustained effect** of treatment over time

VNS Therapy has a **favorable safety profile**

Risk of suicide is **decreased by adding VNS Therapy**

There is **evidence of improved QOL and restored psychosocial functioning**

Compliance is **guaranteed**

With limited treatment options and the morbidity/mortality associated with the disease, **VNS Therapy® is needed in a psychiatrists' therapeutic armamentarium** to treat and manage these difficult to treat patients