

Mitsubishi Tanabe is making a huge mistake:

Why we believe that Neuroderm is a lemon

We believe that Mitsubishi Tanabe and its board need to **immediately** put a hold on the Neuroderm acquisition. We don't know what representations have been made to Mitsubishi Tanabe by Neuroderm or others pushing this acquisition, but our research findings demonstrate the following:

- Neuroderm has misrepresented the **SIZE** of the market, the **RELEVANCE** of their clinical study, and the **EFFECTIVENESS** of their ND0612 pump-delivered drug.
- AbbVie's Duopa/Duodopa pump is already **ESTABLISHED** in the market, has a **SUBSTANTIALLY LOWER** adverse effect rate, conducted its trials on an **APPROPRIATE** subject pool, and did not rely on **SUPPLEMENTARY** oral levodopa or entacapone, to boost its clinical trial results, unlike Neuroderm.
- Neuroderm claims the size of ND0612's target market across the USA and EU is ~350,000 patients. AbbVie's superior pump has targeted the **SAME** market, only capturing ~3,500 patients.
- The ND0612 drug is marketed towards **ADVANCED** stage Parkinson's sufferers, however the efficacy study for the drug was conducted on **EARLY** stage Parkinson's sufferers, which require substantially lower doses of the active drug component in order to be effective. We believe the FDA will closely review the stage 3 trials to ensure ND0612 is tested on an **APPROPRIATE** and **RELEVANT** subject pool.
- Neuroderm's ND0612 delivery pump is made up of **GENERIC COMPONENTS** and presents **ZERO R&D** proprietary value.
- ND0612 is now only being tested for bioequivalence, not efficacy. While this may lead to a speedier FDA approved drug, Mitsubishi Tanabe is meant to be buying Neuroderm for its **TECHNOLOGY**. We see this concession as further evidence of Neuroderm's weak R&D value, which Mitsubishi Tanabe thought it was buying with this acquisition.

We believe that it is important for Japanese businesses, post Toshiba's horrific acquisitions abroad, as well as Mori Seki, and Lixil, to conduct more extensive due diligence in order not to lose investor confidence and capital. We believe that Mitsubishi Tanabe's acquisition of Neuroderm will be regrettable, and the board will have a lot to answer for including regulatory and legal claims.

Viceroy encourages Mitsubishi Tanabe's board, investors and financiers to immediately re-evaluate its proposal to acquire Neuroderm, as we believe its product is un-investible and will lead to a complete write-off.

***Viceroy values Neuroderm's at its most recent book value of
~\$4.87 per share, representing an EV of \$0.***

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Summary

On 24 July 2017, Neuroderm entered into a definitive agreement to be acquired by Mitsubishi Tanabe Pharma Corporation for **\$39 per share, totaling ~\$1.1b, in cash**. This is approximately all of Mitsubishi Tanabe's \$800m cash balance and all or most of its expected free cash flow for 2017. Viceroy believes this is a terrible acquisition for Mitsubishi Tanabe.

Viceroy values Neuroderm at its most recent book value of ~\$130m or \$4.87 a share, which is representative of Neuroderm's cash on hand. This represents a \$0 EV and an 88% discount to Mitsubishi Tanabe's proposed acquisition price.

Mitsubishi Tanabe, its shareholders and its financiers should walk away from this deal. Viceroy believes that Neuroderm's drug is un-investable – an acquisition will not net any return on investment for Mitsubishi Tanabe. We liken this poor due diligence deal to Toshiba's Westinghouse unit's acquisition of CB&I Stone & Webster, which resulted in a write-down of \$6.1b.

Neuroderm (NASDAQ: NDRM) is a clinical stage pharmaceutical company primarily involved in development of treatment for the symptoms of Parkinson's disease; specifically the ND0612 product line.

According to clinical trials and medical data; neither ND0612H nor ND0612L can provide sufficient levodopa to function as a standalone treatment for Parkinson's disease.

Both products require entacapone to augment plasma levodopa levels and the concurrent use of oral levodopa. Entacapone and oral LC/CD is marketed by NDRM's competitor Novartis.

ND0612's phase 2 clinical trials showed significant issues:

1. High incidence rate of adverse effects associated with the ND0612 delivery system.
2. Clinical trial subjects were at an earlier stage of Parkinson's Disease than that of Neuroderm's target market, thus leading to favorable clinical trial results.
3. Oral levodopa was used **as needed** in the efficacy trial, raising questions as to whether the trial efficacy results are useful **at all**.
4. 16 hour out-patient results are extrapolated from 8-hour in-patient results, raising concerns as to other possibly data-mined outcomes.
5. There was no true blind test.

In light of the above, Neuroderm's post phase 2 clinical trial meeting with the FDA resulted in a change of approach from efficacy to bioavailability/bioequivalence, meaning the ND0612 drug must now be shown to be "as good as" and not "better than" current available treatments. Viceroy finds it obscure that ND0612 must be 'as good as' the oral LC/CD alternative which was used 'as needed' by ND0612 patients.

Further, ND0612's direct competitor, AbbVie's Duodopa (marketed as Duopa in the US) appears to be a safer and more effective product based on clinical trial data as well as already being in the market.

*In any case, Neuroderm's target market is **substantially** smaller than sell-side analysts predict as not all stages of Parkinson's would require the ND0612 product.*

Viceroy believes:

1. Medical professionals and Parkinson's sufferers may be hesitant to prescribe or use the implant given the redundant nature of the drug, high costs, and high incident rate of adverse effects.
2. Neuroderm's product may struggle to obtain FDA approval.
3. Neuroderm's product may struggle to generate sales in a market where oral LD/CD product *must* be used in conjunction with their own product to show bioequivalency to the very same competitor's product. The proposition is nonsensical.
4. Neuroderm's product may struggle to outperform its direct competition.

Mitsubishi should pursue its growth targets elsewhere and conduct more extensive due diligence. We base our opinion and target price on Neuroderm's available clinical and financial data and have consulted extensively with specialists in the field.

Background

Neuroderm (NASDAQ: NDRM) is a clinical stage pharmaceutical company primarily involved in development of treatment for the symptoms of Parkinson's disorder. These products are ND0612H and ND0612L, (H and L denoting high and low dosages respectively). While their product pipeline includes other products, these are largely immaterial to Neuroderm's implied value.

Neuroderm's success and survival is largely dependent on the performance of the ND0612 product.

ND0612 is a liquid formulation of Levodopa/Carbidopa (LD/CD), an existing compound of L-DOPA amino acid and carbidopa used to treat the symptoms of Parkinson's disease – namely; loss of coordination, trembling of extremities, trembling of the face and slowness of movement. This is referred to as OFF time. ND0612 is administered intravenously through a patch-pump or small belt pump that releases LD/CD to the bloodstream.

Levodopa's use in Parkinson's Disease symptom management is well established however administration of levodopa through the duodenum is relatively novel. Administering compounds through the duodenum brings into play risk of infection and complication both in the initial surgery and during ongoing use. ND0612's competitor in the field is AbbVie's Duopa/Duodopa which received marketing approval and orphan drug status from the FDA in 2015.

Clinical test result analysis

Neuroderm's clinical phase 2 trial results are underwhelming especially when compared to oral LD/CD and other products in the field. Our main concerns around the phase 2 trials are:

1. Trial subjects were at an earlier stage of Parkinson's disease than Neuroderm's target market of 'Severe Parkinson's Disease Patients', thus requiring lower doses to reduce OFF time.
2. Inadequate stand-alone dosage – Only high dosage ND0612 combined with entacapone sold under the name Comtan performs better than oral LD/CD, and only on patients at an earlier stage of Parkinson's disease than Neuroderm's target market.
3. Significantly higher incidence of adverse effects compared to competitor AbbVie's Duopa/Duodopa pump.
4. Continued dependence on oral LD/CD as needed to produce favorable OFF time.
5. Lack of placebo and double blind.

Inadequate stand-alone dosage

*Plasma-levodopa concentration of subjects using either of Neuroderm's products **alone** (both ND0612L and ND0612H) are **far below** the dose required to adequately treat the symptoms of Parkinson's disease better than the existing treatment. Generic oral LD/CD treatment is already widely used and accepted.*

Neuroderm's clinical trial results clearly demonstrate that ND0612 produces inferior results when compared to oral LD/CD. Levodopa treatment efficiency is assessed through the concentration of levodopa in the blood plasma of a subject and decrease in OFF time.

As the disease progresses, higher levels of levodopa are required to manage dyskinesia symptoms in check over periods of time.¹

This is supported by both Neuroderm's test results and existing literature on Parkinson's disease treatment with levodopa:

¹ Wearing Off

<https://www.parkinsonswa.org.au/what-is-parkinsons/wearing-off/>

- Neither ND0612 product achieves the plasma-levodopa levels of the baseline oral LD/CD treatment, the current generic competitor.

Table 2. Mean (\pm SD) Levodopa pharmacokinetic parameters

Study Group	Treatment	PK Parameter		
		Modified Fluctuation Index [p value vs Baseline Day2]	C _{max} [ng/mL]	AUC (0-8h) [ng.h/mL]
Low-Dose ND0612 N = 9	Baseline Oral LD/CD	535 (\pm 30.9)	1820 (\pm 498.5)	5743 (\pm 2169.6)
	ND0612 Low carbidopa concentration	103 (\pm 43.8) [p<0.0001]	618 (\pm 495.8)	2,487 (\pm 873.8)
	ND0612 High carbidopa concentration	65 (\pm 43.8) [p<0.0001]	487 (\pm 103.6)	2,434 (\pm 441.7)
	ND0612 High carbidopa concentration + Entacapone	73 (\pm 46.2) [p<0.0001]	604 (\pm 105.8)	2,923 (\pm 517.8)
High-Dose ND0612 N = 7	Baseline Oral LD/CD	535 (\pm 30.9)	2262 (\pm 726.0)	8414 (\pm 3566.2)
	ND0612 Low carbidopa concentration	97 (\pm 49.6) [p<0.0001]	1,355 (\pm 269.8)	6,466 (\pm 1,404.4)
	ND0612 High carbidopa concentration	130 (\pm 49.6) [p<0.0001]	1,454 (\pm 269.7)	7,549 (\pm 1,620.5)
	ND0612 High carbidopa concentration + Entacapone	111 (\pm 49.0) [p<0.0001]	1,844 (\pm 381.9)	8,853 (\pm 1,557.7)

Baseline Modified fluctuation Index (Model's root mean square estimate [MSE]) of fluctuation calculated for all 16 patients in both groups.

Figure 1 – Mean Levodopa Pharmacokinetic Parameters (ND0612)²

Note: C_{max} - maximum (or peak) serum concentration that a drug achieves in a specified test area of the body after the drug has been administered.³ In this case it refers to the plasma-levodopa concentration.

AUC - a summary or index measure of cumulative response to treatment over the observation period.⁴

² Stable levodopa plasma levels with ND0612 (levodopa/carbidopa for subcutaneous infusion) in patients with Parkinson's Disease with motor fluctuations

http://neuroderm.com/wp-content/uploads/2016/09/03_Poster_presented_at_the_World_Parkinsons_Congress_Oregon_2016_ND0612_003.pdf

³ Tracy TS (2004). "Pharmacokinetics". In Stitzel RE, Craig CF. *Modern pharmacology with clinical applications*. Hagerstown, MD: Lippincott Williams & Wilkins. p. 49. ISBN 0-7817-3762-1.

⁴ Area Under the Curve Analysis and Other Analysis Strategies for Repeated Measures Clinical Trials
http://www.stat.ncsu.edu/information/library/mimeo.archive/isms_1983_1453.pdf

2. CURS test results significantly improve past plasma-levodopa levels of ~1024ng/ml for patients in stages 3-4 of Parkinson's Disease.

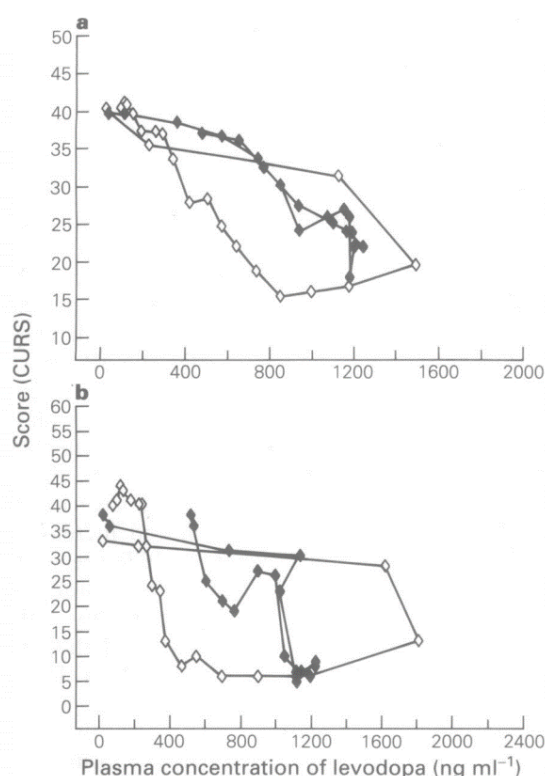


Figure 3 Plasma drug concentration-effect relationship after administration of IR-levodopa (100 mg levodopa/ 25 mg benserazide ◇) and CR-levodopa (300 mg levodopa/75 mg benserazide ◆) (a) mean values, $n = 10$ (b) patient 6.

Figure 2 – Plasma / drug concentration-effect relationship (ND0612)⁵

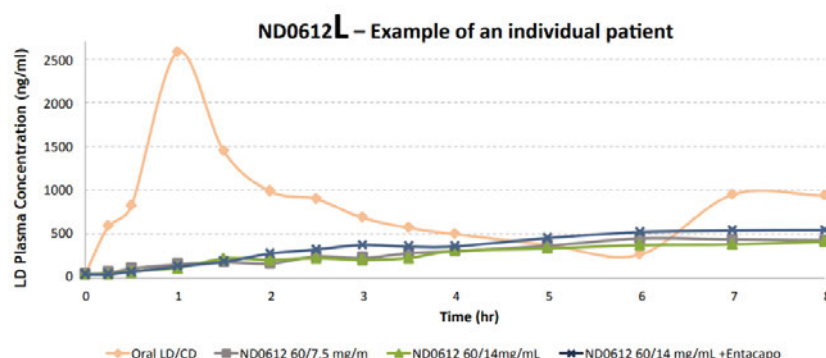
Note: CURS is a test measuring the severity of dyskinesia produced by Parkinson's disease. Lower scores indicate a lesser intensity of dyskinesia.

As visualized above, Parkinson's Disease related dyskinesia symptoms drop off significantly after reaching a threshold plasma/levodopa level.

⁵ Concentration-effect relationship of levodopa in patients with Parkinson's disease after oral administration of an immediate release and a controlled release formulation
<http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2125.1995.tb04407.x/pdf>

3. ND0612L plasma-levodopa levels stabilize below minimum levels required to incite a reduction in Parkinson's related dyskinesia in advanced stage Parkinson's disease.

(a)



(b)

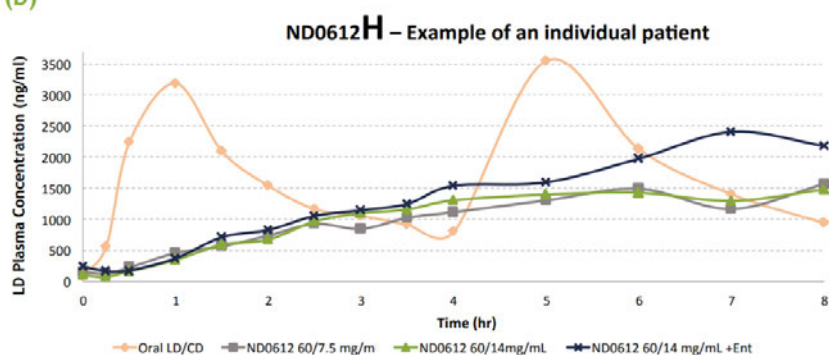


Figure 3 – Levodopa plasma concentration over time – comparative results⁶

Note: Benserazide is not used in the USA, Carbidopa is used instead.⁷

ND0612L and ND0612H were only able to achieve 487ng/mL and 1454ng/mL plasma respectively compared to 1820ng/mL and 2262ng/mL baseline oral LD/CD. Thus, only ND0612H is able to maintain equivalent plasma-levodopa levels to significantly affect Parkinson's symptoms and only through the use of entacapone.

Entacapone is sold under the name Comtan and is marketed by Swiss brand Novartis Pharmaceutical Corporation⁸, the same company that markets Stalevo⁹, an oral LD/CD product.

For Neuroderm's products to achieve comparable results to their competitor they must be used in conjunction with that same competitor's product.

⁶ ND0612 (levodopa/carbidopa for subcutaneous infusion) achieves stable levodopa plasma levels <http://neuroderm.com/PDF/Poster-presented-at-theMDS-Vancouver-2017-ND0612-003-004.pdf>

⁷ Parkinson's disease: carbidopa, nausea, and dyskinesia <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4238750/>

⁸ Comtan® (Entacapone) <https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/comtan.pdf>

⁹ STALEVO- carbidopa, levodopa and entacapone tablet, film coated - Novartis Pharmaceuticals Corporation <http://medlibrary.org/lib/rx/meds/stalevo-1/>

In light of the above we believe:

1. **ND0612L may not achieve plasma-levodopa levels high enough to produce results meaningful enough to justify cost and switch from oral LD/CD.**
2. **Neither ND0612L nor ND0612H are capable of reaching similar levodopa levels or efficacy of treatment as the existing treatment when used alone.**

We question whether medical professionals and patients would elect for a treatment requiring significant additional discomfort and cost when the current oral generic is available.

We question the usefulness of the ND0612L line of products which may not result in significant change in levodopa levels.

Phase 2 efficacy study performed on irrelevant test group

Severity of Parkinson's and its symptoms are characterized into progressive stages by using the Hoehn & Yahr scale; from 1 to 5 with 5 being the most severe and 1 being the least. For context, sufferers diagnosed as being past stage 3 are generally no longer independent.¹⁰

Neuroderm's phase 2 efficacy study was conducted on 38 individuals, not a single one of which had a Hoehn & Yahr stage past stage 3. In fact, such subjects were intentionally excluded from the study!

Table 3: Baseline characteristics of the enrolled patients			
	R1 (24 hours) (N=19)	R2 (14 hours) (N=19)	Overall (N=38)
Age (years); mean (SD)	63.0 (10.07)	64.0 (8.47)	63.5 (9.19)
Sex; n (%) male	12 (63.2)	14 (73.7)	26 (68.4)
Modified Hoehn and Yahr Stage; n (%)			
1	1 (5.3)	-	1 (2.6)
1.5	-	1 (5.3)	1 (2.6)
2	13 (68.4)	11 (57.9)	24 (63.2)
2.5	4 (21.1)	5 (26.3)	9 (23.7)
3	1 (5.3)	2 (10.5)	3 (7.9)
Years since PD diagnosis; mean (SD)	10.7 (5.5)	12.2 (5.0)	11.5 (5.2)
Years since motor fluctuations onset; mean (SD)	5.7 (6.9)	5.5 (4.8)	5.6 (5.9)
Years since dyskinesia onset	3.1 (2.7)	4.2 (3.4)	3.7 (3.1)
Daily OFF time (hours); mean (SD)	5.6 (2.1)	5.0 (2.4)	5.3 (2.2)
Daily Time with Moderate or Severe Dyskinesia; mean (SD)	1.2 (2.8)	2.5 (3.7)	1.9 (3.3)
UPDRS Part III (motor) score; mean (SD)	37.4 (14.5)	37.3 (13.3)	37.3 (13.7)
Levodopa dose (mg); mean (SD)	1135.8 (818.0)	1054.1 (567.3)	1094.9 (695.5)
Frequency levodopa dosing; mean (SD)	6.8 (3.2)	6.9 (2.2)	6.9 (2.7)

Figure 4 –ND0612 subject baseline characteristics – phase 2 trials

¹⁰ The FIVE Stages of Parkinson's Disease

<http://parkinsonsresource.org/wp-content/uploads/2012/01/The-FIVE-Stages-of-Parkinsons-Disease.pdf>

Inclusion
Male and female (30 - 80 years) patients with a diagnosis of PD
Hoehn & Yahr (during ON) of stage ≤ 3
≥ 2.5 hours of OFF time per day.
Predictable and well defined early morning OFF periods and a 'good' early morning response to levodopa.
Taking ≥ 4 levodopa doses per day (≥ 3 doses/day of IPX-066)
Have attempted to take at least 2 other classes of PD medications in a therapeutic dose for at least 30 consecutive days each. All PD medications had to have been stable for ≥ 30 days prior to the start of the study.

Figure 5 – ND0612 subject inclusion criteria – phase 2 trials ¹¹

In fact, most subjects (63.2%) were in the second stage of the disease. Most patients in phases 1 to 3 are generally on oral LD/CD and would be reluctant to incur the cost and risk of the ND0612 device.

We believe that this choice of subjects skews the results positively as progressively greater amounts of levodopa are required to mitigate Parkinson's symptoms as the disease progresses through the stages, this is known as the wearing off effect.¹²

Neuroderm's stated target market is patients suffering severe or advanced Parkinson's symptoms.¹³ How can the efficacy of the product in that regard be analyzed based on subjects who are not at that stage of the disease?

Adverse events

We draw your attention to the following table detailing adverse effects of ND0612 during phase 2 clinical trials.

Table 1: Incidence of Adverse events with ND0612			
Adverse event	Regimen 1 N=19	Regimen 2 N=19	Overall N=38
Any AE; n (%)	15 (79%)	14 (74%)	29 (76%)
Serious AE; n (%)	2 (11%)	2 (11%)	4 (11%)
Discontinued due to an AE	1 (5%)	1 (5%)	2 (5%)
Frequent AEs; n (%)			
Infusion site nodules	11 (58%)	7 (37%)	18 (47%)
Infusion site bruising	4 (21%)	3 (16%)	7 (18%)
Infusion site erythema	5 (26%)	2 (11%)	7 (18%)
Infusion site hemorrhage	2 (11%)	3 (16%)	5 (13%)

Figure 6 – Incidence of adverse effects with ND0612 ¹⁴

¹¹ Baseline characteristics of the population

<http://neuroderm.com/PDF/Poster-presented-at-the-MDS-Vancouver-2017-ND0612-006-Baseline-characteristics.pdf>

¹² Wearing Off

<https://www.parkinsonswa.org.au/what-is-parkinsons/wearing-off/>

¹³ Neuroderm presentation – Jefferies 2015 Global Healthcare Conference

<http://www.jefferies.com/CMSFiles/Jefferies.com/files/NeuroDerm%20revised%20V4.pdf>

¹⁴ Safety, efficacy, and tolerability of continuous SC LD/CD (ND0612H) infusion in PD patients with motor fluctuations

<http://neuroderm.com/PDF/Poster-presented-at-theMDS-Vancouver-2017-ND0612-006-results.pdf>

*76% of subjects experienced adverse effects with 11% experiencing **serious adverse effects**. At least 47% of subjects experienced adverse effects due to the infusion delivery method.*

Neuroderm's clinical study results are inferior to that of direct competitor AbbVie's Duodopa:

	AbbVie Duodopa	Neuroderm ND0612
Infusion LD/CD	Yes	Yes
Oral LD/CD	No	Yes
Formulation	Duodopa	ND0612H
Number of subjects	62	38
AE (number, %)	53.2%	76%
Mean decrease in OFF time	-2.34 hours	-3.50 hours

While Duopa study results show an inferior mean decrease in OFF time, they did so:

- **Without the assistance of supplementary oral LD/CD OR entacapone.** As discussed earlier, Neuroderm has not shown whether ND0612 has been able to produce results without supplementary oral LD/CD.
- **With subjects classified as having advanced stage Parkinson's Disease. Neuroderm's clinical study subjects were classified at an earlier, more mild stage of Parkinson's Disease.**

The number of adverse effects is also a substantial 20 percentage points lower. We question whether a product marketed to improve quality of life will succeed against an established competitor with undoubtedly superior adverse effects.

We remind our readers that this was a 28-day study; what sort of effects can be expected in long term treatment?

Would patients opt for an auxiliary treatment with a higher risk of adverse effects compared to an existing product?

16-hour of results normalized from initial 8-hour measurements for a 24-hour drug

The stated aim of the ND0612 product line is:

ND0612H has been designed to provide continuous subcutaneous delivery of an adjustable, high dose, LD/CD formulation to significantly improve motor and non-motor complications in patients refractory to oral LD/CD. ND0612H's subcutaneous administration – utilizing a convenient belt-pump (resembling the administration of insulin to diabetic patients) – allows patients to receive continuous LD/CD therapy on a 24 hour basis, thus avoiding morning “off” time and ensuring a good night's sleep.

Figure 7 –Neuroderm defined purpose of ND0612¹⁵

The January 2017 poster on the phase 2 results of ND0612H show that the OFF-time measurements for the trial were observed during an 8-hour in-patient period and then normalized over the remaining 16 hours of the day. **In effect, the results of these 8 hours were used to extrapolate the results of the following 16 hours.**

Note below that the R2 dosing regimen only uses a 14-hour infusion cycle.

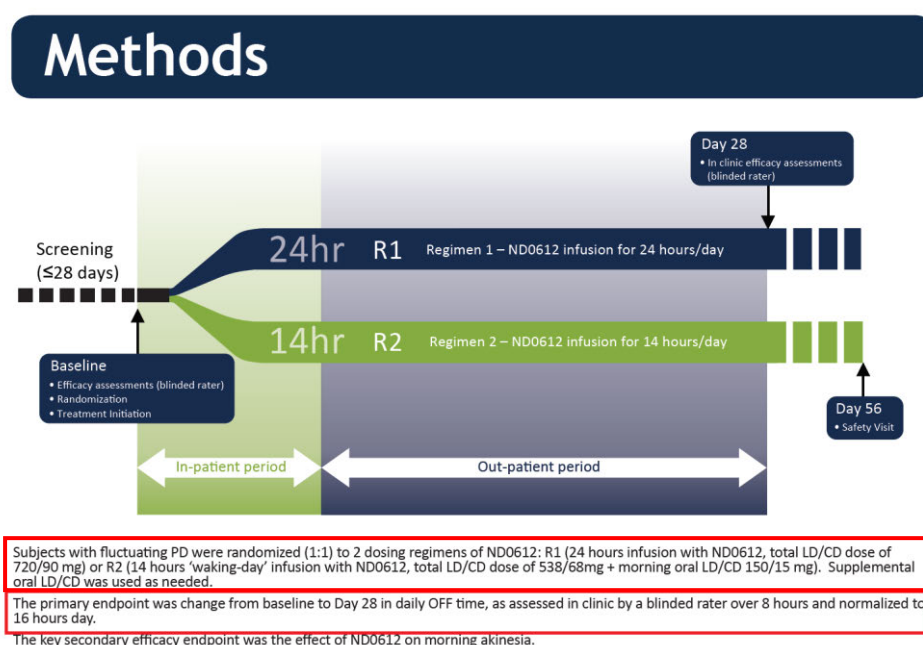


Figure 8 –ND0612 dosing regimen – phase 2 trials¹⁶

This is contrary to the response of Parkinson's symptoms to LD/CD treatment. ND0612 is designed to provide continuous 24-hour levodopa therapy. To extrapolate 16 hours of results from an 8-hour observation period is consistent with the drug's stated purpose and does not provide a full picture of its performance.

¹⁵ ND0612H for severe PD

<http://neuroderm.com/nd0650-for-severe-pd/>

¹⁶ Safety, efficacy and tolerability of continuous SC LD/CD (ND0612H) infusion in PD patients with motor fluctuations

<http://neuroderm.com/PDF/Poster-presented-at-theMDS-Vancouver-2017-ND0612-006-results.pdf>

Further, we note from the above Figure 8 that:

1. No placebo was administered for the efficacy analysis, contrary to other tests of prospective Parkinson's therapy clinical tests.¹⁷
2. Given the lack of a placebo, the rater (the clinician who administers and records the effects of the drug) would have known that the patient was receiving treatment of some kind.

With no placebo in place the rater could only have been blinded regarding the dosage of the therapy, not whether the therapy was being administered. In this sense, the study was practically open label.

For reference, previous studies into the effects of Parkinson's symptom therapy incorporated both double blind and placebo methods (i.e. the rater and the subject do not know who is receiving the active/placebo drug).¹⁸

Oral levodopa treatment still required

Our concern over the phase 2 efficacy and tolerability trial results is from the following passages:

Subjects with fluctuating PD were randomized (1:1) to 2 dosing regimens of ND0612: R1 (24 hours infusion with ND0612, total LD/CD dose of 720/90 mg) or R2 (14 hours 'waking-day' infusion with ND0612, total LD/CD dose of 538/68mg + morning oral LD/CD 150/15 mg). Supplemental oral LD/CD was used as needed.

- The average oral levodopa dosing frequency reduced from 6.9 times/day at baseline to 2.3 times/day at Day 28. Likewise, mean oral levodopa doses decreased from 1100 mg at baseline to 330 mg at Day 28.

Figure 9 – Safety, efficacy and tolerability of continuous SC LD/CD (ND0612H) ¹⁹

As per our above section regarding clinical study subject selection, the subjects for the trial were chosen to be at or below phase 3 of Parkinson's progression, in other words, not the intended market! Neuroderm's product is marketed towards subjects with advanced Parkinson's Disease, generally accepted to be stages 4 to stage 5.²⁰ We question the use of ND0612H's clinical study as demonstration of its efficacy in light of the fact that supplemental oral LD/CD was used *as needed* throughout the trial. In the same poster, Neuroderm claims that 42% of subjects in one test arm achieved 0 hours of OFF time at the end of the 28 days, however oral levodopa use had not stopped but only decreased. Seen in this light, ND0612 is more appropriately a complementary therapy to oral LD/CD, albeit a costly one.

Why would patients outlay substantial additional costs for a supplementary drug with a clinically proven disposition to adverse effects?

¹⁷ Levodopa—carbidopa intestinal gel in advanced Parkinson's disease open-label study: Interim results
<https://www.ncbi.nlm.nih.gov/pubmed/23287001>

¹⁸ Levodopa and the Progression of Parkinson's Disease
<http://www.nejm.org/doi/full/10.1056/NEJMoa033447>

¹⁹ Safety, efficacy and tolerability of continuous SC LD/CD (ND0612H) infusion in PD patients with motor fluctuations
<http://neuroderm.com/PDF/Poster-presented-at-theMDS-Vancouver-2017-ND0612-006-results.pdf>

²⁰ Treatment of Advanced Parkinson's Disease
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3038575/pdf/PD2010-480260.pdf>

FDA advice for bioavailability/bioequivalence study in lieu of clinical efficacy

Neuroderm mentioned the results of its end-of-phase 2 with the FDA. While the announcement was heralded as a success by Neuroderm and a signal of a positive relationship with the FDA, we believe otherwise.

Key takeaways:

1. Suspension of ongoing phase 3 trials for ND0612L, discontinued preparations to initiate phase 3 clinical trials.
2. Continuation of BeyoND clinical phase 2 trial with addition of 50 new participants.²¹
3. Focus on a bioavailability/bio equivalency regulatory route instead of the previously pursued efficacy development route.

NDRM announced its intent to pursue a comparative bioavailability regulatory path for ND0612H instead of pursuing an efficacy study. We draw your attention to the following:

As defined by the FDA; Bioavailability:

"the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action"

Bioequivalence:

"the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study"

We believe that the shift from efficacy to bioavailability/bioequivalence is a conscious attempt to avoid head-to-head comparison of ND0612H to existing treatments.

²¹ Neuroderm (NDRM) to Discontinue ND0612H Phase III, Suspend iNDiGO After FDA Meeting
<http://www.biospace.com/News/neuroderm-to-discontinue-nd0612h-phase-iii-suspend/440861>

A Parexel report into phase 3 clinical trial failures revealed that 50% of phase 3 clinical trial failures did so on the basis of lack of efficacy.

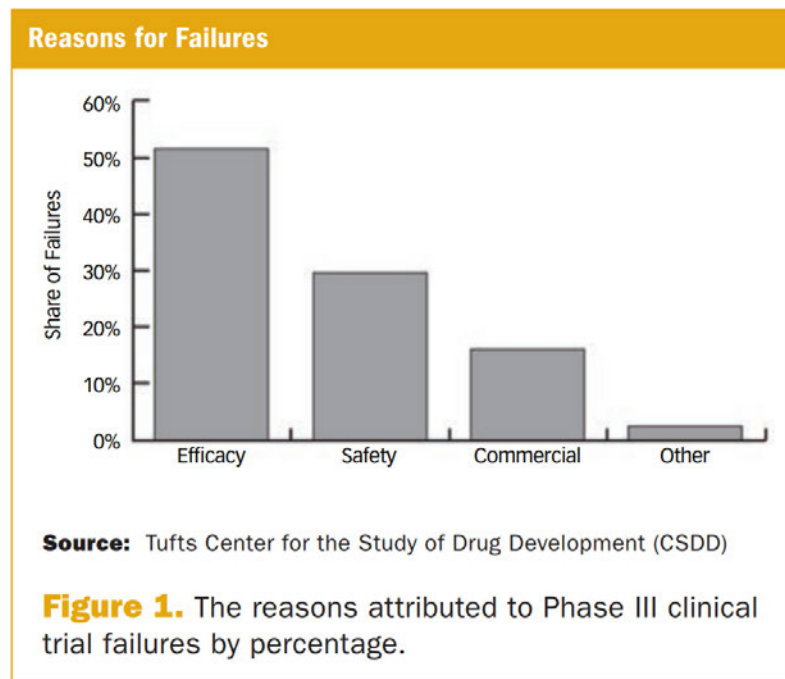


Figure 10 –Reasons attributed to Phase 3 clinical trial failures²²

The evidence we listed above regarding inadequate dosage as well as the dependence of phase 2 trial results on ongoing usage of oral levodopa may explain the FDA's suggestion of a bioavailability/bio-efficiency approach.

²² Phase 3 Trial Failures: Costly But Preventable
https://www.parexel.com/files/5014/7274/5573/ACT_Article.pdf

Key takeaways

- Plasma-levodopa concentration of subjects using either of Neuroderm's ND0612 products taken alone (both ND0612L and ND0612H) are far below the dose required to adequately treat the symptoms of Parkinson's disease better than the existing treatment. Generic oral LD/CD treatment is already widely used, likely far cheaper and accepted.
- 76% of subjects experienced adverse effects with 11% experiencing serious adverse effects. At least 47% of subjects experienced adverse effects due to the infusion delivery method. Would patients opt for an auxiliary treatment with almost guaranteed discomfort?
- Phase 2 results were obtained from subjects at stages 1 to 3 of Parkinson's disease. These subjects would not ordinarily fall under Neuroderm's advance stage Parkinson's Disease market segment target. Additionally, as earlier stage Parkinson's Disease sufferers require lower levodopa levels to incite a reduction in OFF-time, Neuroderm's clinical trial results would be significantly superior to real-world scenarios.
- Phase 2 results of ND0612H show that the OFF-time measurements for the trial were observed during an 8-hour in-patient period and then extrapolated over the following 16 hours. This is contrary to the response of Parkinson's symptoms to LD/CD treatment. For a drug designed to reduce overall off time, this normalization of results taints the results and at worst invalidates them.
- No placebo was administered, contrary to other tests of prospective Parkinson's therapy clinical tests.
- Both products require entacapone to augment plasma levodopa levels and the concurrent use of oral levodopa. Entacapone and oral LC/CD (under the names Comtan™ & Stalevo™ respectively) are already accepted treatments marketed by NDRM's competitor Novartis.
- Oral LD/CD was used as needed in the trial making it difficult to find the standalone efficacy of ND0612.

ND0612's target market

The following table is from a 2015 Neuroderm presentation at Jefferies Global Healthcare conference. It displays the estimated number of severe or advanced Parkinson's Disease patients, the target market for both Neuroderm's ND0612 and AbbVie's Duopa/Duodopa.

US & EU	
Total PD patients	2,200,000
Moderate PD patients	~900,000
Severe PD patients	~350,000
DBS new patients/yr	~22,000
Duodopa/Duopa patient base	~3,500
Duodopa/Duopa new patients/yr	~700
Apomorphine patient base**	~4,000
Severe patients not treated with advanced treatments	~>300,000

Figure 11 –ND0612 customer base - Jefferies 2015 Global Healthcare Conference ²³

In 2015, Duodopa obtained FDA approval for marketing in the US as well as orphan drug status²⁴, as the FDA believes that less than 200,000 people in the US are suffering from advanced Parkinson's Disease. The adoption rate for AbbVie's established Duopa/Duodopa pump is extremely low.

According to our calculations (USA Duopa revenues / approximate wholesaler acquisition cost²⁵), there were only an estimated 500 patients using Duopa in the USA in 2016 for a top-line figure of \$37m.

We presume that the causes of this reluctance are surgery requirements, adverse effects and cost. Unfortunately for Neuroderm, these are shared with ND0612.

²³ Neuroderm presentation – Jefferies 2015 Global Healthcare Conference

<http://www.jefferies.com/CMSFiles/Jefferies.com/files/NeuroDerm%20revised%20V4.pdf>

²⁴ AbbVie Announces U.S. FDA Approval of DUOPA

<http://www.prnewswire.com/news-releases/abbvie-announces-us-fda-approval-of-duopa-carbidopa-and-levodopa-enteral-suspension-for-the-treatment-of-motor-fluctuations-in-patients-with-advanced-parkinsons-disease-300018802.html>

²⁵ In Brief: Duopa - A Carbidopa/Levodopa Enteral Suspension for Parkinson's Disease

<https://secure.medicalletter.org/w1474d>

Neuroderm's promotional materials often paint the company as a pioneer in the field and ND0612 as a revolutionary product in the field of Parkinson's Disease symptom treatment. The facts say otherwise: ND0612's concept of a portable continuous-release LD/CD treatment is done better and safer by its competitor AbbVie. We find it hard to digest that patients will respond more favorably to ND0612 than Duopa/Duodopa in any market, US or international.

Lack of proprietary technology

Neuroderm's ND0612 product line is largely comprised of off-the-shelf components.

"...the engine of the pump is off the shelf, and so is the battery..."

- Oded Lieberman (translated), Neuroderm CEO²⁶

Indeed, the ND0612 system uses the Crono Twin ND Belt pump manufactured by CANE S.p.A Medical Technology.



Figure 12 – Crono Twin ND Belt Pump ²⁷

Neuroderm's pump and delivery technology are off the shelf components and will deliver no proprietary R&D value to Mitsubishi Tanabe.

Mitsubishi Tanabe's acquisition of Neuroderm at an implied valuation of ~\$1bn (excl. cash) cannot even be justified as the price for proprietary tech which could perhaps be repurposed for other drugs.

The Cronos pump was BANNED for import from July 29, 2015 to April 22, 2016 into the USA on the basis of the product being 'adulterated', including failure to document repairs and failure in protocols to document complaints.²⁸

During this period of serious quality concerns, Neuroderm was conducting its phase 2 trials.

²⁶ <https://www.calcalist.co.il/markets/articles/0,7340,L-3718990,00.html>

²⁷ Crono Twin Ambulatory Infusion Pump
<http://www.pompeinfusionali.it/wp-content/uploads/Crono-twin-Data-Sheet-.pdf>

²⁸ FDA letter to Cane S.p.A. – 29 July 2017
<https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2015/ucm459305.htm>

Mitsubishi Tanabe is making a huge mistake

Viceroy values Neuroderm at its most recent book value of ~\$130m. This represents an EV of \$0. It also represents a ~88% discount to Mitsubishi Tanabe's proposed acquisition price, and only so because NDRM has net cash on hand.

Viceroy encourages Mitsubishi Tanabe, its shareholders and its financiers to reconsider an acquisition of Neuroderm.