# Back to the future – fast forward

## USD 339 mn Indivior deal highlights pipeline potential

**FOCUS AREA: ALLOSTERIC MODULATORS FOR (RARE) NEUROLOGICAL DISORDERS**

| KEY DATA | | | SIX: ADXN |
|---|---|---|---|
| **MARKET CAPITALIZATION** (CHF MN) | 56 | **SHARE PRICE ON JANUARY 5, 2018** | 3.7 |
| **ENTERPRISE VALUE** (CHF MN) | 49 | **RISK-ADJUSTED NPV PER SHARE** (CHF) * | 12.5 |
| **ESTIMATED CASH** (3 JANUARY 2018) (CHF MN) | 6.7 | **UPSIDE/DOWNSIDE** (%) | 241% |
| **MONTHLY OPERATING EXPENSE** (CHF MN) | 0.3 | **RISK PROFILE** | SPECULATIVE |
| **CASH LIFE** | 2021 | **SUCCESS PROBABILITY LEAD PROJECT** | 20% |
| **BREAK-EVEN** (YEAR) | >2020 | **EMPLOYEES** | 10 |
| **FOUNDED** (YEAR) | 2002 | **LISTED** (YEAR) | 2007 |
| **KEY PRODUCTS:** | **STATUS** | **MAJOR SHAREHOLDERS:** | **(%)** |
| - DIPRAGLURANT-IR (PD-LID**) | PHASE II | - HERCULIS PARTNERS | 3.5 |
| - DIPRAGLURANT-ER (CERVICAL DYSTONIA) | PHASE I | - EXECUTIVE MANAGEMENT *** | 3 |
| - ADX71441 / $GABA_B$ PAM (ADDICTION) | PHASE I | **- FREE FLOAT** | **97** |
| - ADX71149 / MGLU2 PAM (EPILEPSY) | PHASE II | - DAILY VOLUME | 50'100 |
| **UPCOMING CATALYSTS:** | **DATE** | **ANALYST(S):** | BOB POOLER |
| - START PHASE IIA POC DIPRAGLURANT-ER IN DYSTONIA | H1 2018 | | BP@VALUATIONLAB.COM |
| - START PHASE I ADX71441 ($GABA_B$ PAM) IN ADDICTION | H2 2018 | | +41 79 652 67 68 |
| - START 1ST PIVOTAL TRIAL DIPRAGLURANT-IR IN PD-LID** | H2 2018 | | |

* = BASED ON DILUTED # OF SHARES TO RAISE CHF 30 MN; ** PD-LID = PARKINSON'S DISEASE LEVODOPA-INDUCED DYSKINESIA; *** EXCL. LONG-TERM INCENTIVE PLANS
ESTIMATES AS OF 8 JANUARY, 2018 SOURCE: VALUATIONLAB ESTIMATES, ADDEX THERAPEUTICS

Addex is a world leader in the discovery of allosteric modulators, a drug class with the potential to revolutionize the treatment of a vast array of neurological diseases. The strategy is to develop drugs generated from its proprietary allosteric modulation discovery platform in rare diseases where there is orphan drug potential and in parallel find high quality partners for programs with potential in non-orphan disease areas. Addex targets two key orphan drug opportunities: 1) dipraglurant IR in Parkinson's disease levodopa-induced dyskinesia (PD-LID); and 2) dipraglurant ER in focal cervical dystonia. Lucrative strategic partnerships were secured with Indivior for ADX71441 in addiction and Janssen Pharmaceuticals Inc. (JPI) for ADX71149 in epilepsy. In addition, Addex is pursuing a collaboration strategy with academic institutions, patient advocacy groups and governmental organizations to cost effectively advance a number of its programs. Following the cash inflow from Indivior, with estimated cash of CHF 6.7 mn, the cash runway is extended into 2021. We derive a risk-adjusted NPV of CHF 12.5/share (assuming 50% dilution to raise CHF 30 mn), a 7% WACC and a 20% success probability for lead project dipraglurant IR in PD-LID. The risk profile is Speculative given the early stage pipeline, limited cash life, and the necessity to timely attract sufficient funds.

**Key catalysts:**

1) **Start phase IIa POC trial of dipraglurant ER in dystonia (H2 2018):** Results expected in H1 2019 boosting the success probability to 50% from 8%.
2) **Start phase I trial of ADX71441 in addiction (H2 2018):** Results expected in H1 2019. Development is fully funded by Indivior with up to USD 330 mn milestones and tiered royalties up to double digit.
3) **Start 1st pivotal phase III trial of dipraglurant IR in PD-LID (H2 2108):** Subject to secure funding, results are expected in H1 2020. PD-LID is an orphan disease indication in the US allowing for smaller and less expensive pivotal trials, faster review times, and 7 years market exclusivity upon approval.

# Strategy & Cash Position

**Considerable value locked up in existing clinical and preclinical pipeline**

Through its proprietary allosteric modulator discovery platform, Addex Therapeutics has built one of the largest clinical and preclinical portfolios of allosteric modulator compounds targeting a variety of central nervous system (CNS) disorders including Parkinson's disease, dystonia, addiction, Charcot-Marie-Tooth type 1A neuropathy, depression, cognition and other neurological diseases. Addex' compounds are different from conventional small molecule drugs in that they bind to a different site (the "allosteric" site) of the receptors they target, potentially resulting in better efficacy and/or tolerability than conventional drugs. The company's clinical and preclinical projects target areas of high-unmet medical need, often with blockbuster peak sales potential. Unfortunately, after a shortfall in funding in May 2013, Addex was forced to put the majority of its projects on hold and scale down operations substantially. Consequently, there is considerable value locked up in the company's existing clinical and preclinical pipeline, which was highlighted by the recent strategic agreement with Indivior for the development of ADX71441 in addiction worth up to USD 339 mn in upfront, guaranteed research funding and milestones as well as tiered royalties up to double digit.

**New development strategy set to unlock pipeline value**

Under leadership of co-founder, Tim Dyer, the Company completed a massive restructuring plan in 2013/2014, where the intellectual property portfolio and allosteric modulation discovery platform were secured, and the cash burn rate was significantly reduced as well as the headcount (now 10 FTE's). In 2015, the company completed a review of the existing pipeline portfolio, identified key areas and projects to pursue, and strengthened its cash position and board. Addex is now pursuing a strategy of collaboration with Industry, governmental organizations, academics and patient advocacy groups to advance its extensive portfolio of innovative allosteric modulation drugs, with the aim to unlock considerable value from its existing pipeline.

Key components of the new development strategy, include:

A. Focus on rare (orphan) neurological disorders
B. Enhance clinical expertise/development through collaborations
C. Secure and aim resources at projects with substantial value inflection points

**A) Focus on rare neurological disorders**

Addex focuses its own clinical development efforts on "straightforward" neurological indications such as movement disorders or peripheral neuropathy caused by imbalances within the glutamate and GABA pathways, where the company has gathered considerable expertise.

The company has also narrowed its focus on orphan (rare) disease indications. Drug development in rare diseases typically provides close and valuable interaction with regulators and key opinion leaders (KOL's), lower development hurdles and costs, faster development timelines, and incentives such as extended market exclusivity from launch.

Addex will no longer fund projects in the existing pipeline that do not fit these criteria. Attractive allosteric modulator projects outside the targeted orphan disease areas shall

only be pursued after sufficient funding has been secured from a clinical development partner with the relevant expertise. The recent agreement with Indivior is a demonstration of the execution of this strategy.

**Addex' targeted pipeline projects, include:**

1) **Dipraglurant IR** for Parkinson's disease levodopa-induced dyskinesia (PD-LID)
2) **Dipraglurant ER** for non-Parkinsonian dystonia
3) **ADX71441 ($GABA_B$ PAM)** for addiction in collaboration with Indivior
4) **ADX71149 (mGluR2)** for epilepsy in collaboration with JPI.

The first two projects (PD-LID, dystonia) target rare neurological movement disorders caused by imbalances in the glutamate pathway backed by robust scientific rational. These projects have Addex' highest priority, and with relatively little funding, could trigger substantial upside. The latter two projects (addiction, epilepsy) target large indications where an external partner is required. ADX71441 ($GABA_B$ PAM) is partnered with Indivior and targets addiction, with peak sales potential of CHF 1 bn. Addex retains the rights to select compounds from the collaboration for certain indications outside addiction, including Charcot-Marie-Tooth 1a neuropathy (CMT1A). ADX71149 is partnered with JPI and targets major CNS disorders. Proof-of-concept was established as an add-on therapy for treating negative symptoms in schizophrenia. The epilepsy indication has substantial upside potential at zero cost to Addex and can be considered as a "wild card".

**B) Enhance clinical expertise/development through collaborations**

Addex has rebuilt a small team of employees and expert consultants to advance its clinical and preclinical programs, which it complements with multiple academic institution, government organization and patient advocacy group collaborations. Implementation of such a collaborative model as opposed to building out an own clinical development organization, has enabled Addex to efficiently access expertise to advance research and development of its targeted projects at very low cost. Revised development plans for the targeted pipeline projects have been drafted with input from key opinion leaders (KOL's) and therapeutic area focused advisory panels. It is worth noting that in November 2016, Addex appointed biopharmaceutical industry veteran, Roger G. Mills, M.D., as Chief Medical Officer. Dr. Mills was with Acadia Pharmaceuticals for nine years, serving as Executive Vice President, Development and Chief Medical Officer. In this role, he oversaw the largest ever international phase III program in Parkinson's disease psychosis, and led the Company's New Drug Application submission to the US Food and Drug Administration (FDA) for NUPLAZID, which was subsequently approved and remains the first and only medication approved by the FDA in this indication.

Recent examples include the research collaborations for $GABA_B$ PAM with the US National Institute for Drug Abuse (NIDA) for nicotine and cocaine addiction and the US National Institute on Alcohol Abuse and Alcoholism (NIAAA) for alcohol use disorder. In January 2015 Addex announced a partnership with the Dystonia Medical Research Foundation (DMRF) to explore the therapeutic use of dipraglurant in the treatment of dystonia, and in May 2015 Addex established a partnership with the University of Rome to explore the use of dipraglurant in rare genetic forms of dystonia. The company has an ongoing collaboration with the Michael J. Fox Foundation (MJFF), where it has been awarded grants of USD 1.9 mn to advance dipraglurant in PD-LID.

**ADX71449** is being advanced by JPI and Addex is eligible for USD 109 mn in development and regulatory milestones, and low double digit royalties.

**ADX71441** is being advanced by Indivior and Addex is eligible for USD 330 mn in development, regulatory and commercial milestones and tiered royalties up to double digit.

**C) Secure and aim resources at projects with substantial value inflection points**

The core of the new strategy is to secure the resources (clinical and financial) needed to advance the targeted orphan disease projects that create substantial shareholder value in the short and medium term. Development of a targeted project to a next inflection point, such as proof-of-concept (POC), increases the value of such a project considerably, extends out-licensing opportunities, and raises the probability of successful development and commercialization.

Importantly, a substantial amount of non-dilutive (clinical) resources will come from the multiple collaborations with academic institutions, governmental organizations and patient groups to advance the targeted projects.

As part of its strategy to secure the necessary resources to advance its pipeline for the benefit of patients, Addex continues to pursue discussions with potential industry partners. However, Addex does not want to entirely focus on the success of corporate partnerships to advance the clinical pipeline and has identified the projects that it wishes to pursue, and will execute development with or without industry partners. Consequently, additional funds will be raised through capital increases and/or private placements at the cost of dilution. However, dilution should be more than offset by reaching major clinical milestones, which increase value substantially. Ultimately, the company could pursue an M&A strategy on successful development of its targeted projects.

**CHF 338 mn raised since inception**

Since inception Addex has raised CHF 338 mn. CHF 137 mn was raised with the successful IPO in 2007. Prior to the IPO, management raised CHF 106 mn in three separate private funding rounds with prime healthcare investors, including Index Ventures, Sofinnova Partners (round one); TVM Capital (round two); and Roche Ventures and SR One, the venture arm of GSK (round three).

| MONEY RAISED | CHF MN |
|---|---|
| PRE-IPO | 106 |
| IPO (INITIAL PUBLIC OFFERING) | 137 |
| GRANTS | 8 |
| UPFRONT & MILESTONE PAYMENTS | 48 |
| PRIVATE PLACEMENTS | 39 |
| **TOTAL RAISED** | **338** |

ESTIMATES AS OF 8 JANUARY, 2018 SOURCE: VALUATIONLAB, ADDEX THERAPEUTICS

Addex has also been successful in raising substantial funds through private placements with high caliber institutional investors such as Biotechnology Value Fund, Visium Asset Management, Armistice Capital, and Herculis Partners, amounting to a total of CHF 39 mn. Herculis Partners is now a major shareholder owning 3.5% of the share capital.

In 2010 the company received a USD 900,000 grant from the Michael J. Fox Foundation for the funding of the phase IIa proof-of-concept trial of dipraglurant in Parkinson's disease,

followed by a USD 1 mn grant in 2013 for the funding of certain phase III preparation studies and activities. Of this grant USD 150,000 remains available for draw down.

**Addex has a history of high value partnerships with major industry players**

Over time the company received substantial partnering related revenues amounting to CHF 48 mn. CHF 29.1 mn came from the mGluR4 (Parkinson's disease) and ADX63365 (schizophrenia) collaborations with Merck & Co. In 2011 both were discontinued due to an internal portfolio re-prioritization at Merck & Co. following its merger with Schering Plough. CHF 14.4 mn came from the mGluR2 allosteric modulators (ADX71149) collaboration with Janssen Pharmaceuticals Inc. (JPI - a Johnson & Johnson company) for treating major CNS disorders, which started in 2005. This collaboration was the first partner validation of Addex' allosteric modulation discovery platform. Addex is eligible for up to EUR 109 mn of additional milestones upon development and regulatory achievements. Addex will receive low double-digit royalties (we conservatively assume 10%) on sales. JPI successfully completed a phase IIa proof-of-concept of ADX71149 as an add-on to current antipsychotics in schizophrenia patients in 2012. A new major indication for this compound could be an add-on treatment to UCB's first-line epilepsy drug Keppra in treating epilepsy. Keppra's peak sales amounted to USD 1.74 bn one year prior to patent loss in 2009.

**Strong validation of technology platform highlighted by recent grants and deal**

In the past 12 months Addex was awarded two additional grants and secured a strategic partnership, providing strong validation of Addex' technology platform and the company's ability to secure funding of its projects. In January 2017, the MJFF (Michael J. Fox Foundation) awarded a USD 835,000 grant towards the discovery of TrkB PAM's (tyrosine receptor kinase B positive allosteric modulators) as potential novel treatments for Parkinson's disease. The US NIDA (National Institute on Drug Abuse) awarded a USD 5.3 mn grant to support clinical trials of ADX71441 for the treatment of cocaine use disorders in October 2017. And in January 2018 Addex announced a strategic partnership with Indivior to accelerate development of ADX71441 ($GABA_B$ PAM) in addiction, receiving a USD 5 mn upfront, milestone payment of USD 330 mn and tiered royalties up to double digit. Addex will receive USD 4 mn guaranteed research funding over 2 years and retains the rights to advance additional $GABA_B$ PAM's in CMT1A neuropathy.

**Bulk of cash used to build world's most extensive allosteric modulator pipeline**

Addex has been a pioneer in building the infrastructure and developing the expertise for discovering and developing highly selective, oral, small molecule, allosteric modulator drugs. The bulk of the CHF 338 mn raised was spent on building this proprietary discovery platform. In 2012 Addex successfully concluded phase IIa proof-of-concept of dipraglurant IR for treating PD-LID and its partner, JPI successfully completed a phase 2 POC in schizophrenia with ADX71149. The company now has an extensive and valuable pipeline of clinical and preclinical allosteric modulator compounds and a unique chemical library of approximately 85,000 compounds with allosteric characteristics, the value of which is waiting to be unlocked.

**Cash runway extended into 2021 thanks to Indivior strategic partnership**

At the H1 2017 results announcement on September 30th, management maintained its guidance for a "cash runway through 2018" with CHF 3.6 mn cash in the bank and no debt. Assuming a CHF 0.3 mn monthly cash burn in H2 2017 and adding the USD 5 mn (CHF 4.9 mn) upfront payment from Indivior, we estimate a cash position of CHF 6.7 mn extending the cash runway into 2021. This, combined with rigorous cash control, leads us

to believe that the company should have sufficient cash to successfully execute on the first major steps of its development strategy.

**The current cash position allows Addex to conduct:**

- Start and complete a phase IIa proof-of-concept (POC) trial with dipraglurant in focal cervical (neck muscle) dystonia
- Prepare dipraglurant to start pivotal trials in PD-LID

Addex has designed and prepared the development of dipraglurant ER in dystonia in collaboration with the Dystonia Medical Research Foundation (DMRF). Furthermore, the company has designed and prepared the development of dipraglurant IR in PD-LID in collaboration with the Michael J. Fox Foundation. Additional funds will be needed to conduct these trials, which the company plans to raise in 2018. Indivior will fully fund the development of ADX71441 in addiction, triggering potential development and regulatory milestones for Addex.

**Successful funding is last step in Addex' development strategy providing upside**

In the table below we provide an overview of additional funds we believe are needed to advance the targeted pipeline projects. In the next three years Addex will need approximately CHF 47 mn to finance: 1) two pivotal phase III trials of dipraglurant IR (instant-release) in PD-LID, and 2) the phase IIa POC trial of dipraglurant ER (extended-release) in cervical dystonia, the ER formulation, and the first of two pivotal phase III trials needed for dystonia. At the present estimated cash position of CHF 7 mn following the Indivior agreement and available MJFF funding of CHF 0.5 mn, and an expected CHF 10 mn upfront payment in 2020 from a EU/ROW partner for dipraglurant on positive "Study 301" results, an additional CHF 30 mn will be needed to finance these development plans. At the current valuation this would lead to a dilution of around 50% (conservatively assumed in our risk-adjusted NPV calculation). Note: Addex could raise the required CHF 30 mn in several tranches: e.g. CHF 15 mn in H1 2018, and CHF 15 mn on positive POC results in dystonia in H1 2019. POC in dystonia should lead to a considerable rise in the valuation and therefore lead to significantly less dilution than we currently assume.

**R&D EXPENDITURE & FUNDING - OVERVIEW**

ASSUMED R&D EXPENDITURE

| COMPOUND | INDICATION | PHASE | 2018E | 2019E | 2020E | TOTAL |
|---|---|---|---|---|---|---|
| **DIPRAGLURANT IR** | **PD-LID** | TOX & CMC | 3 | 3 | 3 | 8 |
| | (ORPHAN - US) | 1ST US PHASE III (STUDY 301) | 5 | 5 | 5 | 15 |
| | | 2ND US PHASE III (STUDY 302) | | | 5 | 5 |
| | | EXTENSION TRIAL (US) | | | 3 | 3 |
| TOTAL (CHF MN) | | | 8 | 8 | 15 | **30** |
| **DIPRAGLURANT ER** | **DYSTONIA** | PHASE IIA POC (STUDY 202) | 2 | | | 2 |
| | (ORPHAN - GLOBAL) | 1ST PHASE III | | 5 | 5 | 10 |
| | | 2ND PHASE III | | | | 0 |
| | | EXTENSION TRIAL | | | 3 | 3 |
| | | ER FORMULATION | 1 | 1 | | 2 |
| TOTAL (CHF MN) | | | 3 | 6 | 8 | **17** |
| **TOTAL R&D FUNDS REQUIRED** | | | **11** | **14** | **23** | **47** |

SOURCE: VALUATIONLAB ESTIMATES

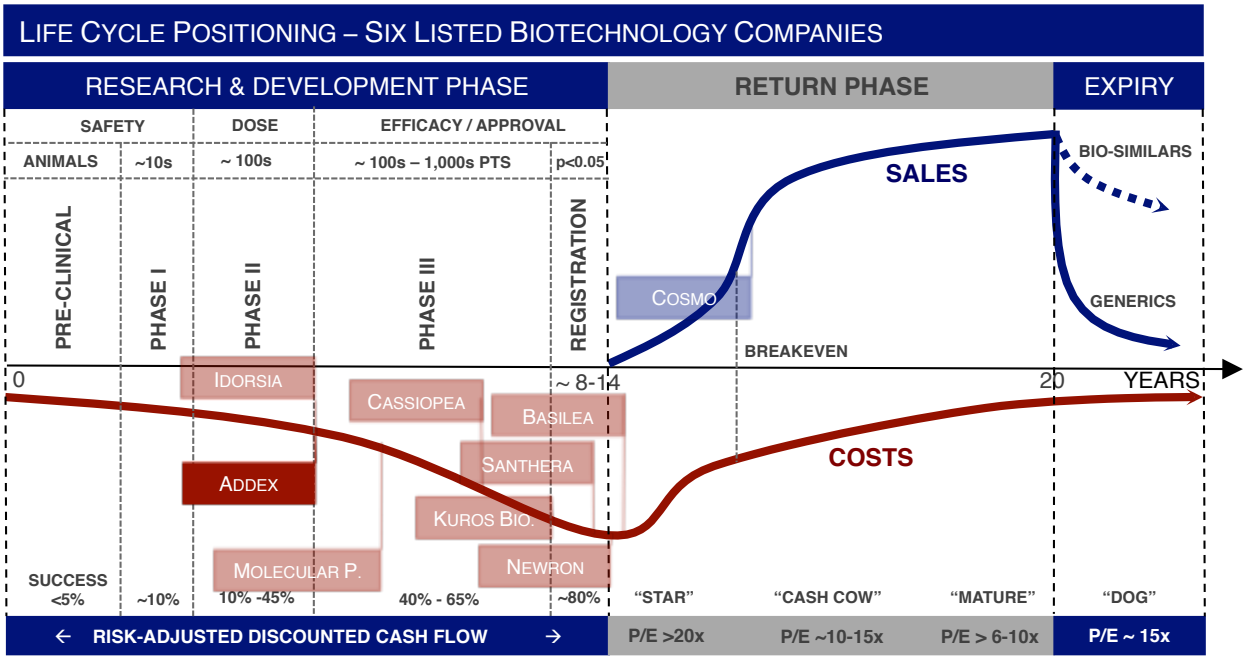
Positive results of the pivotal trials for dipraglurant in PD-LID and dystonia should lead to a jump in valuation and attract a lucrative development and commercialization partnership. In our forecasts we assume a EU/ROW partnership to occur in 2020. The expected upfront, development and sales milestones from a partnership should be sufficient to finance the development of dipraglurant up to commercialization. Moreover, development milestones from Indivior (up to USD 330 mn) and Janssen Pharmaceuticals Inc. (up to

EUR 109 mn) could provide additional funding on reaching certain clinical and regulatory milestones. These potential cash inflows have not been taken into consideration in our financial model.

In our view, successful funding should result in a considerable rise in Addex' market capitalization with the removal of the "financing overhang" to fund its two key phase III development programs, each with blockbuster peak sales potential.

**Life Cycle Positioning - Speculative**

We consider an investment in Addex as Speculative with currently a limited cash runway into 2021. The company has no products on the market that can provide sustainable revenue streams, while the targeted projects are still in an early development stage with a relatively low success probability. Development of these projects is largely dependent on Addex successfully and timely raising sufficient funds through various partnerships and private placements.




SOURCE: VALUATIONLAB

# Valuation Overview

**Risk-adjusted sum-of-parts NPV points to a fair value of CHF 12.5 per share**

We derive a risk-adjusted NPV of CHF 12.5 per share (conservatively assuming a 50% dilution to raise CHF 30 mn) with cash of CHF 0.3 per share (30 June 2017), overhead expenses of CHF 0.3 per share, and a WACC of 7.0%, which reflects the low Swiss interest environment.

**SUM OF PARTS**

| PRODUCT | INDICATION | PEAK SALES (CHF MN) | LAUNCH YEAR (EST) | UNADJUSTED NPV/SHARE (CHF) * | SUCCESS PROBABILITY | RISK-ADJUSTED NPV/SHARE (CHF) * | PERCENTAGE OF TOTAL |
|---|---|---|---|---|---|---|---|
| DIPRAGLURANT-IR (MGLU5 NAM) | PD LEVODOPA-INDUCED DYSKINESIA | 2'067 | 2023 | 42.5 | 20% | **8.5** | 68% |
| DIPRAGLURANT-ER (MGLU5 NAM) | DYSTONIA (NON-PD) | 1'522 | 2024 | 45.5 | 8% | **3.6** | 29% |
| ADX71149 (MGLU2 PAM) | "WILD CARD" TBD | TBD | TBD | TBD | | | |
| ADX71441 (GABA-B PAM) | ADDICTION | 1'018 | 2025 | 15.3 | | | |
| ESTIMATED CASH POSITION (3 JANUARY 2018) | | 7 | | 0.3 | | **0.3** | 2% |
| **TOTAL ASSETS** | | | | 103.6 | | **12.4** | **100%** |
| OVERHEAD EXPENSES | | | | -0.3 | | **-0.3** | |
| **NPV/SHARE (CHF)** | | | | 103.4 | | **12.5** | |
| SHARE PRICE ON JANUARY 07, 2018 | | | | | | 3.9 | |
| PERCENTAGE UPSIDE / (DOWNSIDE) | | | | | | 219% | |

* BASED ON DILUTED NUMBER OF SHARES TO RAISE CHF ~30 MN FOR DIPRAGLURANT DEVELOPMENT PLANS

ESTIMATES AS OF 8 JANUARY, 2018

SOURCE: VALUATIONLAB ESTIMATES

**Addex' valuation currently based on two key value drivers:**

**1) Dipraglurant IR (PD-LID) - Fair value of CHF 8.5 per share**

For dipraglurant IR, the immediate release formulation, we forecast peak sales of CHF ~2 bn for treating Parkinson's disease levodopa-induced dyskinesia (PD-LID) a rare (orphan) disease indication in the US affecting less than 200,000 people, with a 20% success rate based on positive phase IIa proof-of-concept data reported in March 2012. We assume Addex will raise sufficient cash to fully develop dipraglurant IR in PD-LID based on two pivotal phase III trials with the first trial to start in H2 2018. On positive results of the first pivotal trial in 2020, leading to significant value creation, we expect Addex to sign on a EU/ROW development and commercialization partner in return for attractive upfront, development and sales milestones (up to CHF 260mn) and royalty payments (20% on net sales). In 2021 we assume US partnering with up to CHF 370 mn milestones and 25% royalties on sales. We calculate a risk-adjusted NPV of CHF 196 mn for dipraglurant IR in PD-LID with a WACC of 7.0%.

**2) Dipraglurant ER (dystonia) - Fair value of CHF 3.6 per share**

The extended release formulation of dipraglurant targets non-Parkinsonian dystonia, a neurological movement disorder that leads to muscle contractions and awkward postures. A proof-of-concept trial in focal cervical dystonia is planned to start in H2 2018 with results in H1 2019. Peak sales could reach CHF ~1.5 bn with first launches in 2024. With the start of the fully funded phase IIa proof-of-concept (POC) trial of dipraglurant ER cervical dystonia, we have now included this indication in our forecasts with a 10% success rate. Our risk-adjusted NPV amounts to CHF 84 mn, assuming Addex receives up to CHF 530 mn milestone payments from development and commercialization partners with 25% royalties on sales.

**No value contributed to early stage pipeline projects, yet**

We have not accounted for Addex' early stage product pipeline stemming from its proprietary allosteric modulation technology platform due to the current lack of proof-of-concept (POC). These projects could provide substantial upside once they demonstrate POC or are out-licensed to partners providing revenue streams through upfront and clinical

milestone payments and royalties on sales. Addex has secured initial funding through partnerships with academic institutions, governmental organizations and patient group organizations to advance preclinical proof of concept. Positive proof-of-concept in each indication leads to considerable value creation and could attract potential out-licensing partners.

**ADX71441 ($GABA_B$ PAM)** (addiction – alcohol / nicotine / cocaine)
In January 2018 Addex signed a strategic partnership with Indivior for global development of ADX71441, a $GABA_B$ PAM, for addiction worth up to USD 339 mn in upfront, guaranteed research funding and milestones. In addition Addex is eligible for royalties up to double digit. Addex received a USD 5 mn upfront payment and will receive USD 4 mn guaranteed research funding over 2 years. Addex retains rights to advance additional $GABA_B$ PAM's in CMT1A which come from the funded research program. Indivior plans to start a phase I safety trial in H2 2018 with results expected in H1 2019. The company assumes first launches in 2025 and we estimate peak sales could easily reach CHF 1 bn. Previously, a partnership with the US NIAAA and NIDA successfully evaluated ADX71441 in a battery of preclinical models to study its potential to treat alcohol use disorder, Nicotine addiction and cocaine use disorder. In October 2017, Addex was awarded a USD 5.3 mn grant from the NIDA to fund phase I development of ADX71441 for the treatment of cocaine use disorder.

## Sensitivities that can influence our valuation

**Ability to fund key development projects:** The key risk of Addex' investment case relates to the successful completion of the targeted clinical studies to create shareholder value within the projected timelines. With a cash runway into 2021, Addex does not have sufficient funds to develop all its targeted development projects up to partnering and commercialization. Established government, academic and patient group collaborations have already advanced research at a low cost. Substantial additional funds will still be needed to successfully execute the new development strategy. Addex will still need to attract development and commercialization partners for these projects and/or seek funding through capital increases, which leads to dilution, or pursue an M&A strategy.

**Speed of funding:** Next to attracting sufficient funds to execute the new development strategy, the time needed to attract these funds will determine the speed and amount of value creation. Slower than expected funding pushes back development plans, thereby reducing the effective patent life of each project that is delayed, impacting the total value.

**Development and approval risk:** Most projects are still in the early stages of development and therefore bear a high risk of failure. The valuation of Addex is currently based on two projects, dipraglurant IR (PD-LID) and dipraglurant ER (dystonia) with relatively low success probabilities of 20% and 8%, respectively.

**Orphan drug designation (ODD) for dipraglurant IR in PD-LID:** The FDA ODD grant should lower development hurdles, costs and timelines substantially, and provide 7 years US market exclusivity. Adamas' Gocovri, a long-acting amantadine formulation, was the first drug to receive US ODD in PD-LID and was approved in August 2017.

**Pricing and reimbursement:** Following an FDA or EMA approval, dipraglurant must be priced and reimbursed by local health care providers. In the US pricing and reimbursement is typically quite straightforward. In the EU pricing and reimbursement occurs on a country-by-country basis, which can lead to different pricing, reimbursement, and potential market launch delays. With Gocovri approved for PD-LID in the US with annual pricing of USD 28,500/patient, we assume similar pricing for dipraglurant IR if it demonstrates a favorable safety, tolerability and efficacy profile in PD-LID.

**Partnering and commercialization:** With no own sales force, Addex will need commercialization partners or will have to raise additional funds to build an own sales infrastructure. Upfront and sales milestones and royalties on sales from these partners could be lower than our estimates. Furthermore, the launched drugs must be successfully positioned and marketed against existing and upcoming treatments.

**Patent and market exclusivity:** Dipraglurant's is protected by a composition of matter patent which expires in 2025 and a polymorph patent which expires in 2034. Protection beyond this period will rely heavily on potential extensions, formulation patents and market exclusivities. We conservatively assume patent protection for dipraglurant IR in PD-LID until 2034 (excluding any extension) and dipraglurant ER for dystonia until 2034 (excluding any extension).

**External sourcing:** Addex does not have its own manufacturing facilities and is dependent on external sourcing to manufacture dipraglurant.

# Catalysts

## CATALYST TIMELINES

| TIME LINE | PRODUCT | INDICATION | MILESTONE / EVENT | COMMENT | IMPACT (PER SHARE) |
|---|---|---|---|---|---|
| **2018** | | | | | |
| 3 JAN | ADX71441 ($GABA_B$ PAM) | ADDICTION | STRATEGIC PARTNERSHIP | STRATEGIC PARTNERSHIP TO ACCELERATE DEVELOPMENT IN ADDICTION; CHF 5 MN UPFRONT, UP TO CHF 330 MN MILESTONES AND TIERED ROYALTIES UP TO DOUBLE DIGIT; CHF 4 MN RESEARCH FUNDING OVER 2 YEARS | |
| H1 | | | FUND RAISING / PARTNERING | FUND RAISING OR PARTNERING NEEDED FOR ESTIMATED CHF 30 MN TO START PIVOTAL DEVELOPMENT OF DIPRAGLURANT-IR IN PD-LID | |
| H1 | DIPRAGLURANT-ER | CERVICAL DYSTONIA | START PHASE IIA POC | START PHASE IIA POC TRIAL (STUDY 202) IN CERVICAL DYSTONIA | |
| H2 | ADX71441 ($GABA_B$ PAM) | ADDICTION | START PHASE I | START PHASE I SAFETY TRIAL BY PARTNER INDIVIOR | |
| H2 | DIPRAGLURANT-IR | PD-LID | START 1ST PHASE III | START 1ST PIVOTAL PHASE III TRIAL (STUDY 301) - DEPENDENT ON SUFFICIENT FUNDING | + CHF 12.7 |
| **2019** | | | | | |
| H1 | ADX71441 ($GABA_B$ PAM) | ADDICTION | RESULTS PHASE I | RESULTS PHASE I SAFETY TRIAL | |
| H1 | DIPRAGLURANT-ER | CERVICAL DYSTONIA | RESULTS PHASE IIA POC | RESULTS PHASE IIA POC TRIAL (STUDY 202) IN CERVICAL DYSTONIA (FUNDED BY DMRF; IN COLLABORATION WITH DYSTONIA COALITION) | |
| H1 | ADX71441 ($GABA_B$ PAM) | ADDICTION | START PHASE IIA POC | START PHASE IIA POC TRIAL IN ADDICTION BY PARTNER INDIVIOR | + CHF 2.3 |
| **2020** | | | | | |
| H1 | DIPRAGLURANT-IR | PD-LID | RESULTS 1ST PHASE III | TOP LINE RESULTS OF 1ST PIVOTAL PHASE III TRIAL (STUDY 301) | |
| H1 | ADX71441 ($GABA_B$ PAM) | ADDICTION | RESULTS PHASE IIA POC | TOP LINE RESULTS PHASE IIA POC TRIAL IN ADDICTION | |
| H1 | $GABA_B$ PAM | CHARCOT-MARIE-TOOTH 1A | START PHASE I | START PHASE I SAFETY TRIAL | |
| H1 | DIPRAGLURANT-IR | PD-LID | START 2ND PHASE III | START 2ND PIVOTAL PHASE III TRIAL (STUDY 302) | |
| | DIPRAGLURANT-IR | PD-LID | EU/ROW PARTNERING | WE ASSUME EU/ROW PARTNERING ON STUDY 301 TRIGGERING UPFRONT PAYMENT - PARTNER FUNDS EU/ROW DEVELOPMENT | |

SOURCE: ADDEX THERAPEUTICS, VALUATIONLAB ESTIMATES

# Technology & Pipeline

**Addex is uniquely positioned with the largest pipeline of allosteric modulator drugs**

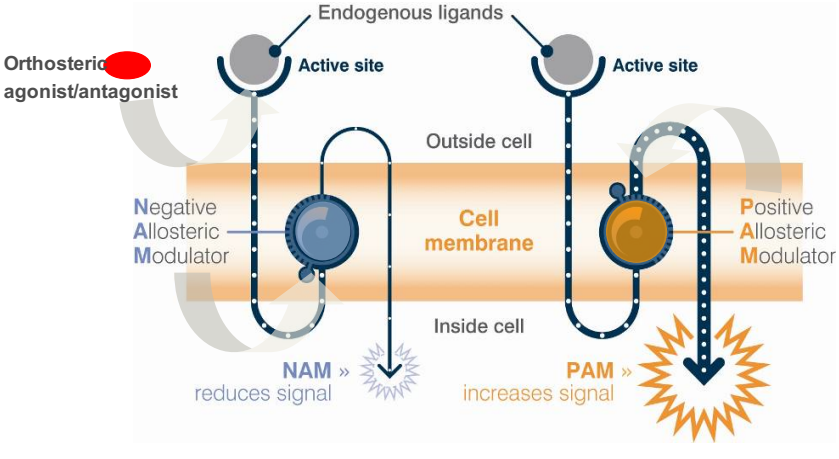
Addex has established a unique chemical library of approximately 85,000 compounds with allosteric characteristics. The library has been assembled from commercial and other non-pharmaceutical sources, with some parts of the library acquired under exclusive agreements. In addition, the company has developed highly specialized biological screening systems to identify and support medicinal chemistry activities for small molecule allosteric modulators drug development. These high-throughput detection systems have enabled Addex to build what we believe to be the largest clinical and preclinical portfolio of allosteric modulator compounds targeting a wide variety of targets, which have broad CNS application.

The company's proprietary allosteric modulator drug discovery platform is based on three key areas:

1. **Allosteric modulation** (better modulatory control of disease mediating receptors)
2. **GPCRs** (G-protein coupled receptors - molecular switches that control the signaling cycle)
3. **Glutamate and GABA pathways** (powerful neurotransmitters in the brain and nervous system that control normal functioning)

**1) Allosteric modulation: conventional "on/off" approach vs. novel "dimmer" switch**

Allosteric modulators are an emerging class of orally available small molecule drugs that may offer a competitive advantage over conventional or so-called "orthosteric" drugs. Conventional drugs work by interacting with receptors on the surface of cells or enzymes, which regulate the rate of chemical reactions within cells that can be imbalanced in disease. By binding to the target receptor site, the primary or "active" orthosteric site, they can either block (turn "off") the physiological function of the protein, or stimulate its effect (turn "on"). The conventional drug approach is similar to an electrical "on/off" switch. Conventional drugs must be able to out-compete naturally occurring substances in order to bind sufficiently to the active site. High receptor affinity is key. However, the continuous stimulation of potentially all receptor sites or a prolonged blockade of receptor functions may lead to unwanted side effects, which is a key problem with conventional orthosteric drugs. In addition, addressing the allosteric site, which unlike the orthosteric site, has not been subject to evolutionary pressure to remain unchanged, offers the unique possibility to identify and develop highly selective compounds.




Source: Addex Therapeutics

Allosteric modulators bind to regulatory sites separate from the active or orthosteric site of the protein, the so-called “allosteric” site. Allosteric drugs rather modulate or control the amount of stimulation of the receptor, similar to an electrical light “dimmer” switch. Naturally occurring substances or conventional drugs can still bind to the active site preserving normal cell function. Because allosteric modulators bind to a different site, they do not have to out-compete naturally occurring substances to bind to the active site, such as conventional drugs do. As a result, allosteric modulators do not need to bind as strongly, or with as much affinity, as conventional orthosteric drugs to be effective, which facilitates discovery and development. Allosteric modulators can decrease the intensity of the signal to the cell interior (negative allosteric modulator or NAM) or increase the intensity of the signal to the cell interior (positive allosteric modulator or PAM). Examples of approved drugs in the market based on allosteric modulation include diazepam (anxiety, insomnia), Amgen’s Sensipar (hyperparathyroidism), and Pfizer’s Selzentry (HIV).

**2) GPCRs are and remain an important target for drug development**

G-protein-coupled receptors (GPCRs) are involved in many important physiological and pathophysiological processes and are considered as one of the most successful therapeutic targets for a broad spectrum of diseases, including cancer, central nervous system disorders, diabetes, inflammation and pain. GPCRs, also known as 7 transmembrane receptors, are the largest family of cell surface receptors and account for approximately 4% of the protein-coding human genome. G-proteins are molecular switches that control the signaling cycle. They are activated by a wide variety of stimulants, including peptide and non-peptide neurotransmitters, hormones, growth factors and lipids. The G-protein system plays a central role in many signaling tasks, in about every organ system, making it an important target for drug development. These receptors are the target of more than 50% of the current therapeutic agents on the market, including more than a quarter of the 100 top-selling drugs.

**3) Targeting glutamate and GABA pathways has potential for many CNS disorders**

Glutamate, like dopamine and serotonin, is a key signaling molecule (neurotransmitter) in the human brain involved in the control of multiple brain functions including mood, memory, perception and motor function. Too much glutamate can lead to seizures and the death of brain cells. Too little glutamate can cause psychosis, coma and death. Glutamate exerts these effects by interacting with many receptors in the brain, especially NMDA, AMPA and kainate receptors.

In addition to these primary receptors, glutamate triggers other receptors, termed metabotropic because they adjust the amount of glutamate that cells release rather than simply turning glutamate transmission on or off. Eight types of metabotropic glutamate receptors (mGluR), each with different functions, have been identified. These mGluRs are attractive targets for drug treatment because of their ability to fine-tune glutamate signaling. Research shows that mGluR drugs have potential for the treatment of schizophrenia, anxiety, Parkinson's disease, fragile X syndrome, Alzheimer's disease, depression and post-traumatic stress disorder. Addex has discovered selective orally available small molecule allosteric modulators for each of the eight subtypes of mGluR.

GABA (gamma-aminobutyric acid) is the main inhibitory neurotransmitter in the central nervous system (CNS). GABA-ergic inhibition is seen at all levels of the CNS, including the hypothalamus, hippocampus, cerebral cortex and cerebellar cortex. GABA pathways are abundant in the brain, with 50% of the inhibitory synapses in the brain being GABA mediated.

**Key advantages of Addex' allosteric modulation drug discovery platform include:**

- Capitalizes on know how of existing "conventional" GPCR targets
- "Undruggable" conventional GPCR targets can now be addressed
- Higher control over the intensity of activation or inhibition
- Greater selectivity and safety than conventional drugs
- Combination use with conventional drugs (different binding site)
- "First-in-class" compounds with strong patent protection

**New development strategy focused on rare neurological movement disorders**

The company will now focus its own clinical development efforts on "straightforward" neurological indications such as movement disorders and peripheral neuropathy caused by the glutamatergic system, where it has extensive expertise, as opposed to complex high risk CNS/psychiatry indications. Addex has also narrowed its focus on rare, so-called orphan disease indications. These are diseases that affect fewer than 200,000 people in the US or less than 1 in 2,000 people in the EU. Drug development in rare diseases typically provides close and valuable interaction with regulators and key opinion leaders (KOL's), lower development hurdles and costs, faster development timelines. Importantly, orphan drug designation (ODD) provides 7 and 10 years market exclusivity from launch in the US and EU, respectively.

**PRODUCT PIPELINE**

| PRODUCT | DRUG CLASS | INDICATION | STATUS | LAUNCH YEAR (EXPECTED) | PARTNER | PEAK SALES |
|---|---|---|---|---|---|---|
| DIPRAGLURANT-IR | MGLUR5 NAM * | PD-LID (PARKINSON'S DISEASE LEVADOPA-INDUCED DYSKINESIA) | PHASE IIB COMPLETED | 2023 (US)<br>2026 (EU/ROW) | | CHF 2 BN |
| DIPRAGLURANT-ER | MGLUR5 NAM | DYSTONIA (NON-PARKINSON) | PHASE I COMPLETED | 2024 | | CHF 1.5 BN |
| ADX71441 | $GABA_B$ PAM | ADDICTION | PHASE I | 2025 | INDIVIOR | CHF 1+ BN |
| ADX71149 | MGLUR2 PAM ** | "WILD CARD" TBD | TBD | TBD | JANSSEN PHARMA. INC. | TBD |
| $GABA_B$ PAM | $GABA_B$ PAM | CMT 1A (CHARCOT-MARIE-TOOTH 1A) | PRECLINICAL | TBD | | CHF 500 MN |
| MGLUR3 PAM/NAM | MGLUR3 PAM/NAM | NEURODEGERATIVE DISORDERS E.G. ALZHEIMER'S, PARKINSON'S | PRECLINICAL | TBD | | TBD |
| MGLUR2 NAM | MGLUR2 NAM | TREATMENT RESISTANT DEPRESSION, COGNITIVE DEFICITS | PRECLINICAL | TBD | | TBD |
| MGLUR7 NAM | MGLUR7 NAM | NEURODEGENERATIVE AND PSYCHIATRIC DISORDERS | PRECLINICAL | TBD | | TBD |
| MGLUR4 PAM | MGLUR4 PAM | ALS (LOU GEHRIG'S) / ORAL MULTIPLE SCLEROSIS | PRECLINICAL | TBD | | TBD |

* NEGATIVE ALLOSTERIC MODULATOR; ** POSITIVE ALLOSTERIC MODULATOR

ESTIMATES AS OF 8 JANUARY, 2018

SOURCE: ADDEX THERAPEUTICS, VALUATIONLAB ESTIMATES

**Addex' targeted pipeline projects include:**

1) **Dipraglurant IR for Parkinson's disease levodopa-induced dyskinesia (PD-LID)** (first-in-class, robust POC, ODD granted)
2) **Dipraglurant ER for non-Parkinsonian dystonia** (first-in-class, strong scientific rational, ODD potential)
3) **ADX71441 ($GABA_B$ PAM) for addiction** (first-in-class, strong scientific rational, POC from baclofen, strategic partnership with Indivior)
4) **ADX71149 collaboration with Janssen Pharmaceuticals Inc.** ("wild card"; epilepsy, substantial upside potential, zero cost)

**In the following section we will provide an in-depth analysis and forecasts for Addex's key driver dipraglurant in PD-LID and dystonia.**

# Forecasts & Sensitivity Analysis

## Dipraglurant (Parkinson's Disease LID & dystonia)

## Product Analysis

**1) PD-LID peak sales of CHF 2 bn - Risk-adjusted NPV of CHF 8.5 per share**

We forecast peak sales of CHF 2 bn for dipraglurant IR (instant release) in PD-LID, assuming market launches in 2023 (US) and 2026 (EU/ROW), a conservative annual treatment cost per patient between CHF 10,000 (EU/ROW) and USD 25,000 (US), and a market penetration peaking at around 19-23% in the target population. Our risk-adjusted NPV amounts to CHF 196 mn, or CHF 8.5 per share with a 20% (phase IIa completed) success probability. We conservatively assume a 50% dilution needed to raise CHF 30 mn to fund the first pivotal phase III trials in PD-LID and dystonia. On successful first pivotal trial results (”Study 301”) in 2020, we assume Addex to sign on a EU/ROW development and commercialization partner for up to CHF 260 mn milestones and 10% sales royalties. On completion of the second pivotal trial (“Study 302”) in 2021 we expect US partnering in return for up to CHF 370 mn milestones and 25% sales royalties (for detailed forecasts see page 29).

**2) Dystonia peak sales of CHF 1.5 bn – Risk-adjusted NPV of CHF 3.6 per share**

For dipraglurant ER (extended release) we forecasts peak sales in dystonia to amount to CHF 1.5 bn with first launches in 2024, and a conservative annual treatment cost per patient of CHF 10,000 (EU/ROW) and USD 25,000 (US), and a market penetration peaking at around 25% in the target population. We expect partnering to occur on completion of phase III development in 2022 with milestones reaching up to CHF 530 mn and 25% sales royalties. We calculate a risk-adjusted NPV of CHF 84 mn or CHF 3.6 per share (assuming a 50% share dilution to raise CHF 30 mn) with an 8% phase IIa POC success probability (for detailed forecasts see page 30).

## 1) PD-LID represents a blockbuster market opportunity

Dipraglurant is a highly selective, oral, brain penetrating, small molecule, metabotropic glutamate receptor-5 negative allosteric modulator (mGluR5 NAM) discovered at Addex. Blockade of mGluR5 has been shown to have anti-Parkinson's disease and anti-dyskinetic effects in a variety of animal models as well as early trials in patients. The drug has potential in multiple indications, including: Parkinson's disease levodopa-induced dyskinesia (PD-LID), non-Parkinsonian dystonia, general anxiety disorder (GAD), Fragile X syndrome (autism), gastro-esophageal reflux disease (GERD/heartburn), migraine pain, depression and addiction.

**Dipraglurant has two separate formulations for two distinct indications:**

1) **Instant Release (IR)** for Parkinson’s disease levodopa-induced dyskinesia (PD-LID)
2) **Extended Release (ER)** for non-Parkinsonian dystonia.

Addex decided to develop dipraglurant IR, in the instant release formulation, first in PD-LID given the significant unmet medical need and early clinical validation seen in targeting mGluR5 in this indication. The company successfully completed a phase IIa proof-of-

concept (POC) trial in PD-LID in 2012 and a receptor occupancy study in healthy volunteers . The phase III pivotal trials are expected to start in H2 2018. Securing sufficient funding to start pivotal trials is key for Addex to unlock considerable value of dipraglurant IR in PD-LID and potentially sign on a lucrative development and commercialization partner after successful completion. Dipraglurant IR would become a first-in-class treatment for PD-LID. At the end of 2013 development of Novartis' mGluR5 NAM mavoglurant (AFQ056) was discontinued in this indication due to lack of efficacy, which seems to be related to the poor profile of the compound rather than the target, as key opinion leaders remain convinced of the validity of the approach.
Additionally, Addex plans to explore the use of dipraglurant, in the extended release formulation, in non-Parkinsonian dystonia, a group of neurological movement disorders. This is based on scientific literature, own preclinical data and the observations made in the PD-LID POC trial, where four patients with dystonia responded positively to dipraglurant compared to three on placebo, despite the trial not powered to show this. In January 2015, Addex established a partnership with the Dystonia Medical Research Foundation (DMRF) to explore the therapeutic use of dipraglurant in the treatment of dystonia and in May 2015 signed the continuation of the collaboration with Dr. Pisani to further explore the potential of dipraglurant in rare genetic forms of dystonia.

**1) PD-LID a major side effect of chronic levodopa use with a high unmet medical need**

As noted, the first indication Addex is pursuing for dipraglurant IR is the acute treatment of levodopa-induced dyskinesia in patients with Parkinson's disease. Recently PD-LID has been recognized as an orphan indication in the US. Parkinson's disease is a slowly progressive degenerative disorder of the central nervous system that initially affects movement (tremor, rigidity, slowness of movement, and difficulty with walking and gait), and later cognition and behavior. Levodopa has been the most widely used and most effective drug to treat Parkinson's disease for over 30 years with most patients noticing an immediate improvement of early motor symptoms.

Dyskinesia (uncontrolled spasmodic or repetitive movements) is a major complication of the chronic treatment of Parkinson's disease. More than half of all persons treated with levodopa or other dopaminergic agonists subsequently develop dyskinesia after only several years on levodopa treatment. Levodopa-induced dyskinesia is a major complication of chronic levodopa use with a negative impact on the long-term treatment of this disease. According to a 2011 Datamonitor survey conducted among key opinion leaders in Parkinson's disease, levodopa-induced dyskinesia is the most important unmet medical need after a disease-modifying agent for Parkinson's disease.

Levodopa-induced dyskinesia is characterized by several distinct forms, including:

- **Chorea** (involuntary, uncontrolled, rapid jerky movements of the arms, legs and face)
- **Dystonia** (prolonged, repetitive muscle contractions causing twisting or jerky movements and unnatural postures, often painful)
- **Athetosis** (uncontrolled, slow, rhythmic twisting movements of hands and feet or other body parts)

Young age of onset, disease severity, duration of therapy, and total dose of levodopa are strongly correlated with the development of dyskinesia. The first manifestations of

dyskinesia are usually dystonic and involve the foot on the same side of the body that is most affected by Parkinson's disease.

With time, dyskinesia may be classified in three main categories:

1. **Peak-dose dyskinesia** (when the level of levodopa reaches its peak in the blood stream)
2. **Diphasic dyskinesia** (also called "onset and end-of-dose dyskinesia" – when the levels of levodopa in the blood stream rise or fall)
3. **Off-period dyskinesia** (during so-called “off-periods” typically in the early morning)

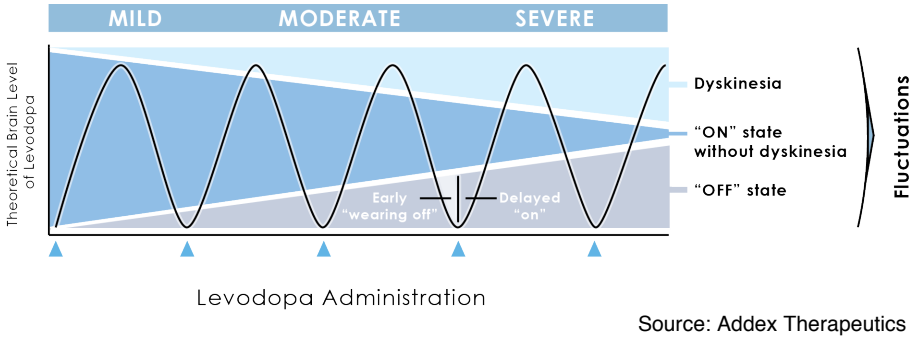
Peak-dose dyskinesia occurs most frequently in roughly 80% of patients, followed by diphasic dyskinesia in 10-20% of patients. Although this classification is very useful in clinical practice, the different types of dyskinesia frequently overlap in a single patient when the disease progresses.

**mGluR5 modulation provides a specific target to treat PD-LID**

Support for a role of group I mGlu (mGlu1 and mGlu5) receptors in the pathogenesis of PD stems from early studies showing that mGluR5 antagonists ameliorate the motor alterations in animal models of parkinsonism and are neuroprotective against MPTP neurotoxicity in animals. However, the major breakthrough in the field of mGlu receptors research in Parkinson’s disease was found in the management of levodopa-induced dyskinesia. Increased postsynaptic mGlu5 receptor density and specific striatal binding with selective mGlu5-receptor ligands are observed in MPTP-lesioned macaques with dyskinesia and in postmortem brains of Parkinsonian patients with dyskinesia. Further evidence for anti-dyskinetic efficacy of mGluR5 antagonists in levodopa-induced dyskinesia comes from preclinical studies in 6-OHDA-lesioned rats and MPTP monkeys. The use of allosteric modulation at this receptor has provided the specificity that is required to limit side effects as well as reduce dyskinesias in animal models and patients.

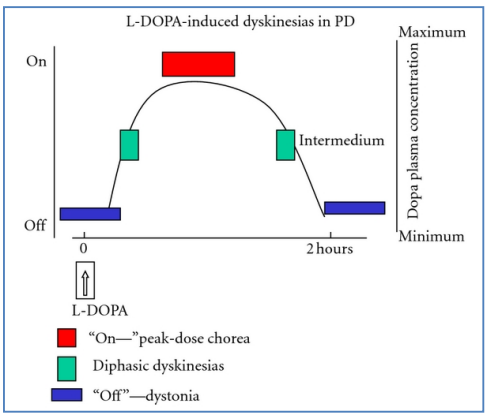
**Dipraglurant IR formulation mimics levodopa uptake to offset peak dose dyskinesia**

Addex has specifically developed an instant release (IR) formulation of dipraglurant that mimics the uptake of levodopa in patients, since peak-dose dyskinesia is the most frequent levodopa-induced dyskinesia. Levodopa has to be given 3-4 times a day due to its relatively short half-life. Peak plasma concentrations are reached 60 to 90 minutes after dosing, when peak-dose dyskinesia occurs.

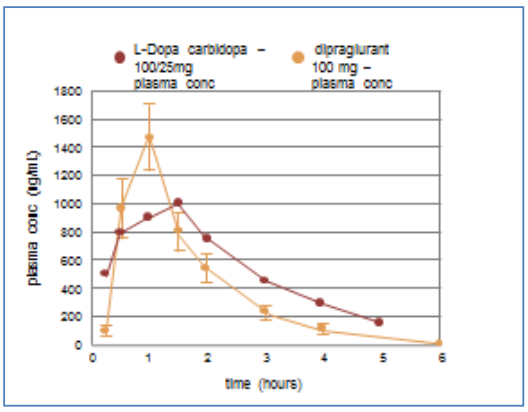



Source: Addex Therapeutics

Dipraglurant IR, which is taken together with levodopa, has a rapid onset of action similar to levodopa, and rapid clearance that reduces unnecessary drug exposure and unwanted side effects. This profile is ideal to offset unwanted peak-dose dyskinesia.




Source: Addex Therapeutics




Source: Addex Therapeutics

**PD-LID complications limit the use of levodopa at the cost of increased rigidity**

In many cases levodopa-induced dyskinesia limits the amount of drug that can be given, curbing symptom relief. Clinical presentations of dyskinesia vary significantly. When severe or painful, they limit therapy but when mild they usually can be tolerated by patients. However, even when mild, it is widely believed that the appearance of dyskinesia foreshadows the development of other, more disabling motor complications. Therefore, even mild dyskinesia may lead the physician to reduce levodopa therapy at the cost of increased rigidity for the patient. As a result, most physicians and patients are hesitant to use levodopa early in the disease. Dopamine agonists and MAO-B inhibitors are typically used in the early stages of disease. However, the majority of PD patients will end up on levodopa and will develop PD-LID.

**More than half of patients affected by PD-LID severely impacting quality of life…**

PD-LID affects roughly half of Parkinson's patients after only 5-10 years of levodopa treatment with the percentage of affected patients increasing over time, up to 90% in patients treated after 10-15 years on levodopa therapy. Half of these patients consider PD-LID as disabling that severely impacts their quality of life. Moreover, the severity of dyskinesia is associated with increasing depression and increased falls.

**… and increasing total treatment costs**

Total medical expenses for treating Parkinson's disease in the US are estimated to amount to USD 23 bn annually or around USD 19,000 per patient per year. After patients develop PD-LID, treatment costs for these patients increase substantially to approximately USD 26,000 per year.

## Statistically significant dipraglurant IR POC results in PD-LID

In 2012 Addex successfully concluded a phase IIa proof-of-concept study in PD-LID, supported by a USD 900,000 grant from the Michael J. Fox Foundation for Parkinson's Research. Top line data showed a statistically significant reduction in dyskinesia, a clinical relevant (>30% reduction in mAIMS (modified Abnormal Involuntary Movement Scale), a 50 minute reduction in "off-time", and 2.3 hours more "on-time" without dyskinesia, all in week 4. Below we present a comprehensive overview of the clinical data Addex reported for dipraglurant IR in its lead indication PD-LID.

**Extensive pre-clinical and early clinical work to establish safety and early POC**

Addex performed extensive pre-clinical work with dipraglurant in animal models that demonstrated early proof-of-concept in Parkinson's disease. The company also conducted three phase I clinical safety trials with a total of 114 healthy persons taking dipraglurant. The drug demonstrated a favorable safety, tolerability and pharmacokinetic profile in "Study 101" (single ascending dose and food effect trial of dipraglurant), "Study 102" (single and multiple ascending dose trial of dipraglurant IR), and "Study 103" (food effect and gender trial with dipraglurant IR).

**Phase IIa POC trial design in patients with moderate-to-severe PD-LID**

In March 2011 Addex moved dipraglurant IR into a phase IIa POC trial in patients with moderate or severe PD-LID. The trial was supported by a USD 900,000 grant from the Michael J. Fox Foundation.

STUDY POPULATION CHARACTERISTICS

| DEMOGRAPHIC AND BACKGROUND CHARACTERISTICS | DIPRAGLURANT IR N = 52 | PLACEBO N = 24 |
|---|---|---|
| AGE IN YEARS (SD) | 64.2 (7.6) | 62.8 (8.3) |
| SEX (%) | MALE: 26 (50%)<br>FEMALE: 26 (50%) | MALE: 12 (50%)<br>FEMALE: 12 (50%) |
| ETHNIC ORIGIN - WHITE (%) | 45 (86.5%) | 22 (91.7%) |
| DURATION OF PD IN YEARS (SD) | 11.62 (4.96) | 11.06 (3.53) |
| TIME OF MOST TROUBLESOME DYSKINESIA (%) | MORNING: 8 (15.4%)<br>MIDDAY: 36 (69.2%)<br>EVENING: 6 (11.5%)<br>NIGHT: 2 (3.8%) | MORNING: 5 (20.8%)<br>MIDDAY: 13 (54.2%)<br>EVENING: 5 (20.8%)<br>NIGHT: 1 (4.2%) |
| PATIENTS WITH DEEP BRAIN STIMULATION (%) | 11 (20.2%) | 2 (8.3%) |
| DURATION OF LEVODOPA TREATMENT IN YEARS (SD) | 9.85 (5.28) | 8.21 (3.8) |
| TOTAL DAILY DOSE OF LEVODOPA IN MG (MEAN SD) | 498.98 (326.84) | 812.96 (383.86) |
| DURATION OF DYSKINESIA HISTORY PRIOR TO SCREENING IN YEARS (SD) | 4.52 (4.0) | 4.19 (2.28) |

SOURCE: ADDEX THERAPEUTICS

The primary endpoint was to evaluate safety and tolerability of dipraglurant IR in PD-LID patients after 4 weeks treatment. Secondary or exploratory endpoints were to evaluate effects on dyskinesia and motor symptoms, and also to identify an effective dose of dipraglurant IR. The randomized (2:1 dipraglurant IR: placebo), double blind, placebo-controlled trial was conducted at 25 sites in the US, Germany, France and Austria, where a total of 83 patients were screened. A total of 76 patients were enrolled in the trial. There was an imbalance in the percentage of patients who had deep brain stimulation with a higher number in the dipraglurant IR group. Covariance analyses did not show an impact of deep brain stimulation on the overall results.

Patients stayed on a constant dose of levodopa (300 – 1,500 mg/day) and were given dipraglurant IR or placebo together with levodopa therapy for a duration of 4 weeks. The patients followed a dose titration regimen. In the first two weeks patients received 50 mg dipraglurant IR up to three times daily until day 14. From day 14 to day 28 the dose was gradually increased to 100 mg three times daily. LID severity was measured on Day 0 (pre-randomization, baseline), and on treatment Days 1 (50 mg, one dose), 14 (100 mg, 3x daily) and 28 (100 mg, 3x daily) by mAIMS (modified Abnormal Involuntary Movement Scale) performed every 30 minutes for 3 hours following a single usual levodopa dose taken around midday. Seven body areas were scored from 0 (no LID) to 4 (severe LID) for a total 28 point score every 30 minutes. Additionally in the home setting, patients collected diary data of "on", "off" and sleep time for 48 hours each week during Week -1 (baseline) and all 4 treatment weeks.

Levodopa efficacy was evaluated during AIMS testing on Days 0, 1, 14, and 28 using UPDRS (Unified Parkinson's Disease Rating Scale) Part III (clinician scored motor evaluation). Overall UPDRS scoring was performed at screening and Day 28. On Day 28, Patient and Clinical Global Impression of Change (PGIC and CGIC) in dyskinesia and Parkinson's disease were collected. After 4 weeks, 47 out of 52 (90%) of the patients on dipraglurant IR completed the trial. Two patients withdrew, while three patients were removed due to protocol violations.

**Primary Endpoint: Safety and Tolerability**

Addex announced the top-line results of the POC trial in March 2012, followed by the presentation of the full data set at the MDS (Movement Disorder Society) annual conference in June 2012.

SUMMARY OF COMMON ADVERSE EVENTS

| TOTAL EVALUATED ADVERSE EVENTS | DIPRAGLURANT IR N = 52 | PLACEBO N = 24 |
|---|---|---|
| ALL ADVERSE EVENTS | 46 (88.5%) | 18 (75%) |
| WORSENING DYSKINESIA (%) | 11 (21.2%)<br>8 (15.3% *) | 3 (12.5%) |
| DIZZINESS (%) | 10 (19.2%) | 3 (12.5%) |
| NAUSEA (%) | 10 (19.2%) | 0 (0%) |
| FATIGUE (%) | 8 (15.4%) | 1 (4.2%) |

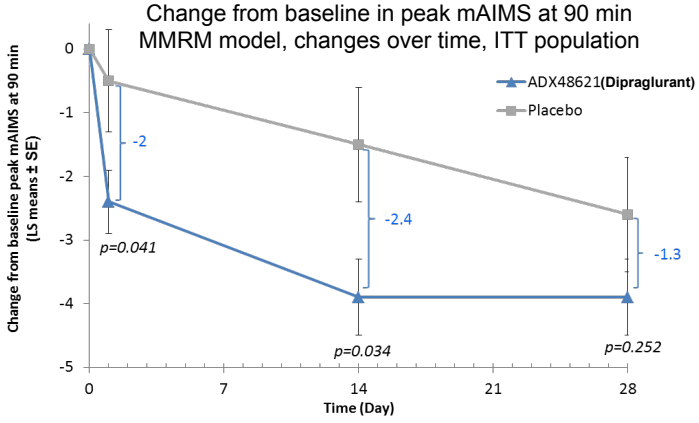
SOURCE: ADDEX THERAPEUTICS

No treatment effects were seen on any of the safety monitoring variables (e.g. ECG, heart rate, blood pressure, hematology, biochemistry). There were slightly more adverse events in the dipraglurant IR treatment group (88.5%) compared to placebo (75%). Most were mild (>80%) and not dose limiting, with the majority of patients completing the dose escalation regimen. Most common adverse events (>10%) in the dipraglurant IR group and (placebo) included: dyskinesia, dizziness, nausea, and fatigue. Three of 11 patients who reported "worsening dyskinesia" did so only in the follow up period (i.e. when not taking dipraglurant). Thus the dyskinesia recurred only after therapy had been stopped. Therefore the adjusted "worsening dyskinesia" is 15.3% for the dipraglurant arm compared to 12.5% for placebo. Adverse events at the 50 mg dose level (week 1 and 2) were less frequent – 53% versus 58% for placebo, than at the 100 mg dose level (week 3 and 4) – 73% versus 63% for placebo.

**Secondary/Exploratory Endpoints: Efficacy**

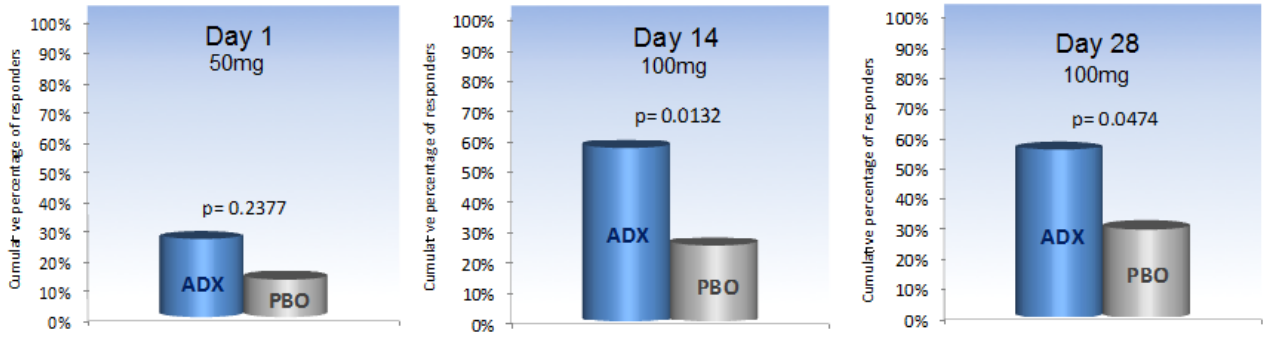
Exploratory efficacy data showed the antidyskinetic effect of dipraglurant IR both on observer evaluated mAIMS and a trend for anti-Parkinsonian effect in the reported data.

**1) Provoked mAIMS at 90 minutes** (impact on peak-dose dyskinesia)



As can be seen in the table above, dipraglurant reduced LID severity by 30%, and had a statistically significant effect on the first day, and reduced dyskinesia compared to placebo at all visits over the 28 days. A 30% reduction in mAIMS is clinically meaningful. One patient was able to hold and read a newspaper for the first time in years. Another patient had improved speech and became more easily intelligible.

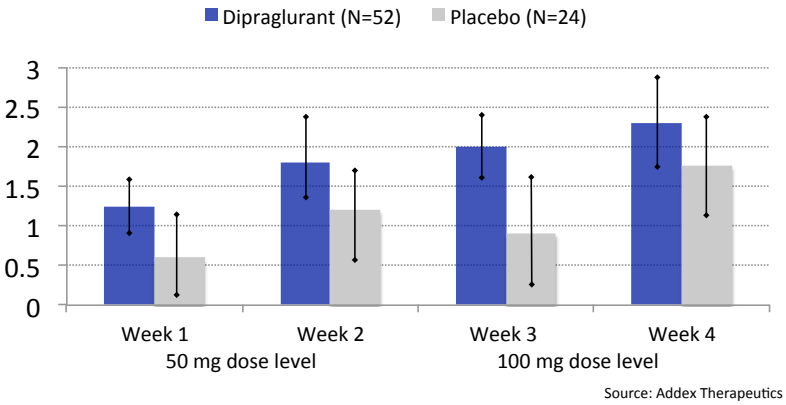
**Cumulative % of patients showing ≥30% change of peak mAIMS from baseline**




Both the 50 and 100 mg doses of dipraglurant IR showed antidyskinetic effect. However in week 4 (day 28) an increased placebo response was seen resulting in a positive, but non-significant impact on peak-dose dyskinesia. A placebo response confounded significance at day 28. The dose titration contributed to the placebo response with patients only on full dosage for the last 7 days. Unfortunately no placebo-mitigating techniques were deployed in the trial, including, no centralized raters, no independent raters, the rater was not blinded to visit number and patients were moderate than severe.

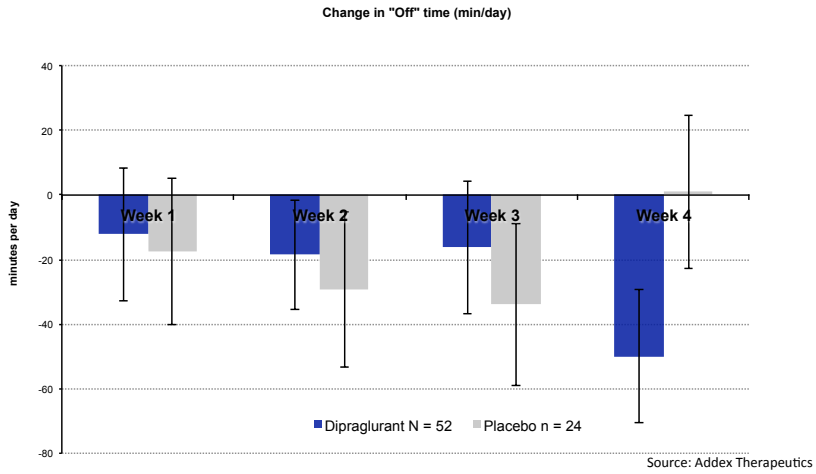
**2) Weekly diary data (48 hours)** (effect on motor fluctuation from patient diaries)

**a) Impact of dipraglurant IR on daily "On" time with no dyskinesia**



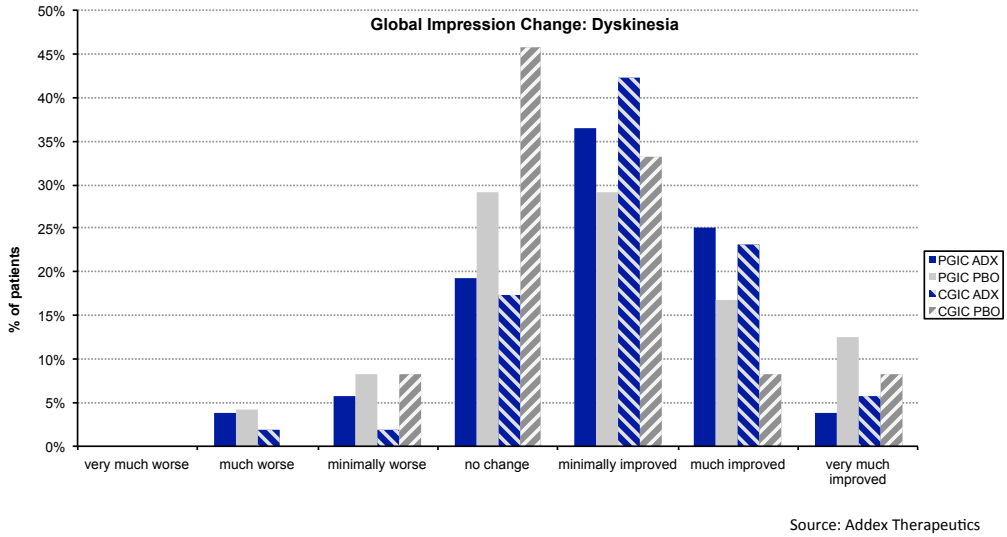

In weeks 1, 2, 3 and 4, dipraglurant IR increased daily "On" time with no dyskinesia by +1,25, + 1.8, +2.0, and + 2.3 hours, respectively.

**b) Impact of dipraglurant IR on daily "Off" time**




Additionally dipraglurant IR reduced daily "Off" time by 50 minutes at week 4. Dipraglurant IR did not affect levodopa efficacy in UPDRS Part III (clinician scored motor evaluation). Both parameters, daily "on" and "off" time, suggest a beneficial effect on motor fluctuation from the weekly patient diaries.

**3) Patient and Clinician Global Impression of Change**




**Patients PGIC:** dipraglurant IR 65.3% vs. placebo 58.4%; p-value = not significant
**Clinicians CGIC:** dipraglurant IR 71.2% vs. placebo 49.6%; p-value = < 0.05

Clinicians rated more improvement for dipraglurant IR treatment for dyskinesia, which reached statistical significance, than patients, where a non-significant trend in favor of dipraglurant IR was seen.

**Conclusion – Phase IIa POC primary endpoint met, further investigation warranted**
The investigators concluded that the study met its primary endpoint in demonstrating good safety and tolerability in patients with PD-LID. Exploratory efficacy data showed antidyskinetic effect as measured by observer evaluated mAIMS and in patient-reported diary data. No negative effect of dipraglurant IR was seen on Parkinson's symptoms, with the suggestion of a beneficial effect on motor fluctuation from patient diaries, which warrants further investigation.

## Future development plans of dipraglurant IR in PD-LID

To further enhance the value of dipraglurant IR, Addex has now set up a comprehensive development plan, in close consultation with key opinion leaders in the field, to explore the use of dipraglurant IR in PD-LID and potentially other indications. The current development plan includes:

**Two pivotal trials required for US registration:**

- **Primary endpoint:** UDysRS (Unified Dyskinesia Rating Scale) score, developed in 2009 specifically for dyskinesia in patients with Parkinson's disease - more sensitive to treatment effect than mAIMS and less prone to placebo response (Goetz 2013); recommended scale by the Movement Disorder Society with an FDA regulatory precedent used in Adamas' pivotal Gocovri trials, which led to approval in PD-LID in August 2017
- **1st pivotal trial "Study 301":** 13 weeks treatment in 170 patients with moderate to severe PD-LID randomized 85 to placebo and 85 on a fixed dose of dipraglurant; primary endpoint: efficacy in reducing LID – change over time in UDysRS (week 13 from baseline); at end of the trial, patients will be enrolled in an open label extension trial; start in H2 2018, top line results in H2 2020
- **2nd pivotal trial "Study 302":** 26 weeks treatment (primary endpoint 13 weeks); 170 patients with moderate to severe PD-LID randomized 85 to placebo and 85 on a fixed dose of dipraglurant; primary endpoint: efficacy in reducing LID – change over time in UDysRS (week 13 from baseline); at end of the trial, patients will be enrolled in an open label extension trial; start 2021, top line results H2 2021
- **Open label extension:** 100 patients exposed for at least 1 year
- **Toxicology:** 6 & 9 month toxicology; 3 month combination toxicology study in one species before large trials start

Addex will continue to interact with the regulatory bodies in 2018 and will consider fast-track / breakthrough therapy designation applications after the first pivotal trial. An NDA (new drug application) submission is projected for mid 2022.

Academic collaborations are ongoing in other disease areas for dipraglurant, including:

- Treatment of migraine
- Treatment resistant depression

# Potential to become a cornerstone treatment in PD-LID

With no cure for Parkinson's disease, the primary aim of therapy is to relieve patients from Parkinson symptoms, keep the patient functional as long as possible, and avoid treatment related side effects as much as possible. These side effects typically develop after 4–10 years of levodopa therapy, and affect approximately 50-75% of all patients. The "wearing-off" effect is the most common type, and "delayed-on," "no-on," and "on-off" fluctuations, as well as dyskinesia (in roughly 40% of patients) and cognitive worsening, may also develop as the disease progresses. Collectively, motor fluctuations represent a significant source of disability in advanced Parkinson's patients, and reducing these is a major goal of patient management. Adjunctive medications, including dopamine agonists, anticholinergics, MAO-B inhibitors, and COMT inhibitors, each may reduce the frequency or duration of "off" periods, but none does so completely, and each contributes its own side effects which may limit optimal dosing.

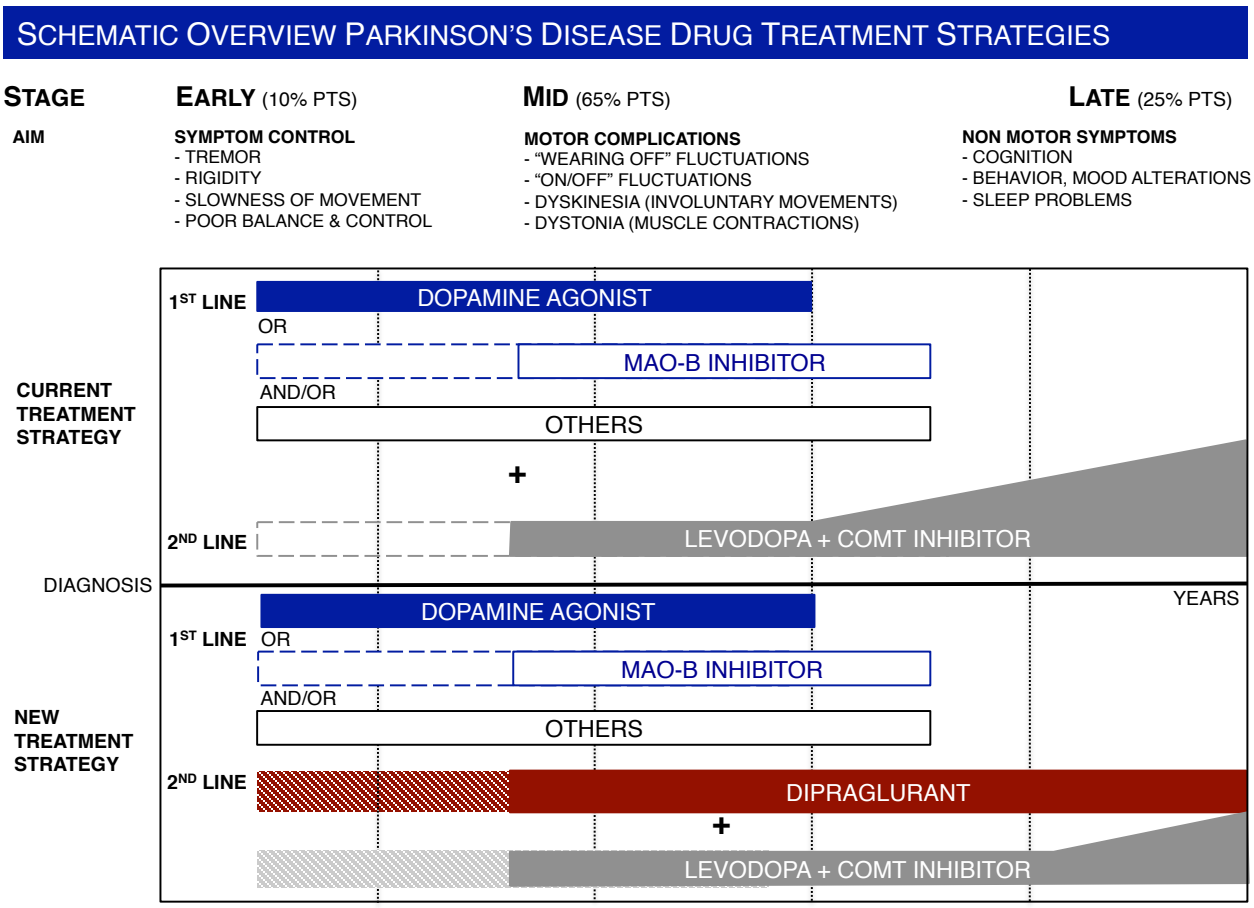
**Therapies aim to delay and limit levodopa use to avoid appearance of dyskinesia**

These problems have led to the development of strategies, which aim to limit or delay the onset of levodopa-related complications and have become the key drivers for the Parkinson's disease market. Dopamine agonists and MAO-B inhibitors are primarily given in the early stages of disease to delay the use of levodopa. As the disease progresses, patients are then given levodopa, at the lowest effective dose. With further disease progression the dose of levodopa usually has to be increased to maintain control of Parkinson symptoms, however, often at the cost of levodopa-induced side effects such as dyskinesia.

**Potential to use levodopa earlier in treatment in combination with dipraglurant IR**

We believe dipraglurant IR has such a promising profile in that it has the potential to reduce levodopa-induced dyskinesia without worsening Parkinson symptoms. Moreover, mGluR5 NAM, MPEP has demonstrated a delay in the on-set of dyskinesia in the MPTP monkey model. As a result, dipraglurant IR could be given to patients early in disease on top of mainstay levodopa to potentially delay the occurrence and reduce the onset of PD-LID after prolonged levodopa use. Consequently, physicians would be able to use levodopa, the most effective Parkinson's treatment to control symptoms and keep patients functional as long as possible, early in the disease, without the risk of patients developing PD-LID after only several years into treatment.

SCHEMATIC OVERVIEW PARKINSON'S DISEASE DRUG TREATMENT STRATEGIES




SOURCE: VALUATIONLAB

**Challenge is to find drugs that treat PD-LID but do not worsen Parkinson symptoms**

Current treatments leave significant room for improvement both in terms of sustained efficacy and safety/tolerability. The challenge is to find drugs that treat PD-LID but do not worsen Parkinson symptoms and demonstrate maintenance of effect for a sufficient

duration of time. Novartis departure from the field with its mGluR5 inhibitor, mavoglurant (AFQ056), at the end of 2013 due to lack of efficacy leaves Addex' dipraglurant IR as the best in class compound for treating PD-LID.

In August 2017, Adamas received FDA approval for Gocovri, a sustained release formulation of amantadine, for treating PD-LID. Although Gocovri is the first ever specific treatment for PD-LID, with an annual treatment cost per patient, the drug has considerable side effects, including falling asleep during activities of daily life, suicidality and depression, and hallucinations and psychotic behavior.

**Other compounds in development for treating PD-LID include:**

- **Eltoprazine** (5HT1a/1b partial agonist) from Amarantus BioScience is a small molecule drug, which is enrolling patients in a phase IIb dosing trial with results due in 2016. Management targets USD 750 mn peak sales for PD-LID in the US alone (we are more conservative with our dipraglurant IR PD-LID forecast of USD 460 mn in the US) and has applied for orphan drug designation in the US. Eltoprazine is also being evaluated in a number of other neurology-focused indications including ADHD (attention deficit hyperactivity disorder) and cognition.
- **AVP-923** (dextromethorphan/quinidine) from Avanir Pharmaceuticals is a fixed dose combination therapy that started enrolling 16 patients with PD-LID in a phase IIa POC trial in 2013. AVP-923's lead indication is agitation in patients with Alzheimer's disease (in phase III). AVP-923 use may be limited due to certain cardiovascular risks and drug interactions. In 2014, Otsuka Pharmaceutical acquired Avanir for USD 3.5 bn.
- **AQW051** (alpha7 nicotinic receptor) from Novartis has shown promise in pre-clinical animal models of PD-LID in MPTP monkeys. This compound may be the follow-up of Novartis' mavoglurant (AFQ056), also an mGluR5 NAM like dipraglurant that was discontinued in PD-LID in 2014 due to the lack of efficacy. No safety concerns were reported.

## 2) Non-Parkinsonian dystonia another significant opportunity

A second major indication for Addex' dipraglurant ER, in the extended release formulation, is for treating non-Parkinsonian dystonia's. Dystonia is a hyperkinetic movement disorder characterized by involuntary and sustained muscle contractions that produce repetitive abnormal, sometimes painful, movements and positions (postures). The movements may resemble a tremor. Dystonia is often initiated or worsened by voluntary movements, and symptoms may overflow into adjacent muscles. There are multiple types of dystonia and numerous diseases and conditions may cause dystonia.

Dystonia is classified by:

1) **Clinical characteristics:** such as age onset, body distribution, nature of symptoms, associated features such as neurological symptoms
2) **Cause:** primary (idiopathic or genetic/hereditary) or secondary (induced by drugs (e.g. neuroleptics), toxins (e.g. lead poisoning), infection, or metabolic disorders

Dystonia can affect a single part of the body (focal), multiple areas (segmental) or the whole body (generalized). Clinicians use these classifications to guide diagnosis and treatment. Specific information on the prevalence of dystonia has been difficult to establish

due to different methodologies for case ascertainment. A meta-analysis points to a prevalence of primary dystonia of 16.43 per 100,000. An estimated 300,000 people in the United States have been diagnosed with a dystonia of some type.

**Cause unknown but excess glutamate release a common underlying mechanism**
The precise cause of primary dystonia is unknown. Dystonia is thought to be caused by an abnormality in or damage to the central nervous system, likely originating in those parts of the brain concerned with motor function, such as the basal ganglia, and the GABA (gamma-aminobutyric acid) producing Purkinje neurons located in the cerebellum. There may be abnormalities in the brain's ability to process a group of chemicals called neurotransmitters that help cells in the brain communicate with each other. There also may be abnormalities in the way the brain processes information and generates commands to move. In many cases it may involve some genetic predisposition towards the disorder combined with environmental conditions. Nevertheless, all have a common underlying mechanism: an excess glutamate release in brain regions controlling movement.

**Non-Parkinsonian dystonia's – no viable treatments available**
Currently, there are no medications to prevent dystonia or slow its progression. There are, however, several treatment options that can ease some of the symptoms of dystonia, so physicians can select a therapeutic approach based on each individual's symptoms.

Current non-medical treatment options for dystonia include:

- **Physical intervention:** such as physical therapy and massage, including sensory biofeedback techniques (effects questionable).
- **Surgery:** such as denervation of selected muscles to provide relief (irreversible) or deep brain stimulation for severe generalized dystonia's, which reduces severity of symptoms by approximately 50%, but significantly varies between individuals with DYT1 patients benefiting most.

Several medications are used to treat dystonia in an effort to find a combination that is effective for a specific person. Not all patients respond well to the same medications. Medications that have had positive results in some dystonia patients include:

- **Anticholinergics:** which block the effects of the neurotransmitter acetylcholine may provide some relief, such as benzatropine and trihexyphenidyl; sedation and memory loss limit their usefulness at higher doses and in older patients.
- **Anticonvulsants:** such as clonazepam, diazepam or carbamazepine that regulate the neurotransmitter GABA; drowsiness is their common side effect.
- **Muscle relaxants:** Baclofen continuously delivered by a pump placed in the abdomen is used to treat patients exhibiting muscle spasticity along with dystonia.
- **Botox injections:** into dystonic muscles can reduce spasms for 1 to 4 months. However, repeated injections become less effective due to production of neutralizing antibodies. Dysport (by Ipsen) is a next-generation injection approved to treat cervical (neck muscles) dystonia.

**Potential to treat dystonia backed by pre-clinical models and in PD-LID patients**
Dipraglurant has the potential to reduce excess glutamate release in the brain regions controlling movement, by inhibiting mGluR5 receptor activity. Dipraglurant has shown positive anti-dystonia effect in multiple animal models as well as in Parkinson's patients. Dipraglurant has demonstrated encouraging results in animal models such as the PD-LID

MPTP monkey (drug-induced dyskinesia with features of dystonia); the DYT1 mouse model (genetic generalized dystonia); and the Tottering mouse model (paroxysmal dystonia).

Importantly, in the phase IIa POC trial of dipraglurant IR in patients with PD-LID, seven patients that also had dystonia, experienced a positive effect after 4 weeks treatment. This was the first early evidence of efficacy in humans with dystonia, and supports Addex decision to explore the use of dipraglurant in dystonia.

**Clinical trial program dipraglurant ER in dystonia**

- **Phase II POC trial H1 2018:** Addex plans to start a phase IIa POC trial ("Study 202" in patients with focal cervical dystonia. The study design currently defined in collaboration with Dr. Jinnah and the DMRF is expected to have an adaptive design in 10 patients with an escalating dose of dipraglurant, one-day protocol in the same patient – possibility to follow up with repeated dosing (funding of approximately CHF 0.5 mn required).

Orphan drug designation and a phase III trial design is under discussion with an advisory panel of KOL's in the field of dystonia.

# Forecasts & Sensitivity Analysis

## DIPRAGLURANT-IR (MGLUR5 NAM) - FINANCIAL FORECASTS FOR PARKINSON'S DISEASE

| | |
|---|---|
| **INDICATION** | PARKINSON'S DISEASE: ACUTE TREATMENT OF MODERATE-TO-SEVERE LEVODOPA INDUCED DYSKINESIA |
| **DOSAGE** | 3-4 TIMES DAILY 50-100 MG (PAIRED WITH LEVODOPA USE TO REDUCE SPIKES) |
| **PRICE** | ANNUAL PRICE PER PATIENT: EU/ROW: CHF 10,000; US: USD 25,000 (CONSERVATIVE PRICING: GOCOVRI USD ~28,000; NUPLAZID USD 24,000; INGREZZA USD 63,300 ) |
| **STANDARD OF CARE** | ADAMAS' GOCOVRI 1ST APPROVED PD-LID DRUG; CURRENT STANDARD OF CARE IS TO DELAY USE OF LEVODOPA WITH DOPAMINE AGONISTS/MAO-B INHIBITORS |
| **UNIQUE SELLING POINT** | SECOND DRUG ON THE MARKET TO TREAT DYSKINESIA CAUSED BY CHRONIC LEVODOPA TREATMENT WITH IMPROVED PROFILE COMPARED TO GOCOVRI |

### 7PS ANALYSIS

| | |
|---|---|
| **PATENT** | JUNE 2025 (COMPOSITION OF MATTER) EP1765795 GRANTED 2013; UP TO 2034 (POLYMORPH PATENTS) FILED 2015; 7 YEARS US ORPHAN DRUG EXCLUSIVITY |
| **PHASE** | PHASE IIA COMPLETED, 1ST PIVOTAL PHASE III TRIAL PLANNED FOR H2 2018; DEVELOPMENT DEPENDS ON SUFFICIENT FUNDING (OR PARTNERING) |
| **PATHWAY** | SAME PATHWAY AS GOCOVRI IN US (ODD): REDUCING DYSKINESIA & "OFF-TIME" & IMPROVING "ON-TIME"; EU/ROW LARGER PATIENT POPULATION (NOT ODD) |
| **PATIENT** | REAL IMPROVEMENT IN QUALITY OF LIFE OF PATIENT WITH LESS DEBILITATING DYSKINESIA LOWERING THE NEED FOR OUTSIDE HELP |
| **PHYSICIAN** | PATIENTS CAN BE GIVEN MAINSTAY LEVODOPA EARLIER AND MORE AGGRESSIVELY EXTENDING THE TIME THIS EFFECTIVE TREATMENT CAN BE GIVEN |
| **PAYER** | REDUCTION OF DYSKINESIA DELAYS AND SIGNIFICANTLY LOWERS COSTS OF OUTPATIENT CARE, NURSING HOMES OR HOSPITALIZATION |
| **PARTNER** | MJFF * FUNDED PHASE IIA AND PARTIALLY PHASE IIB/III - PARTNERING OPPORTUNISTIC; WE ASSUME ADDEX TO RAISE FUNDS FOR PIVOTAL TRIALS AND THEN PARTNER |

### REVENUE MODEL

| **EUROPE / REST OF WORLD** | **2017E** | **2018E** | **2019E** | **2020E** | **2021E** | **2022E** | **2023E** | **2024E** | **2025E** | **2026E** | **2027E** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| NUMBER OF PARKINSON'S PATIENTS (MN) | 3.6 | 3.6 | 3.7 | 3.8 | 3.9 | 3.9 | 4.0 | 4.1 | 4.2 | 4.3 | 4.3 |
| GROWTH (%) | 2% | 2% | 2% | 2% | 2% | 2% | 2% | 2% | 2% | 2% | 2% |
| PATIENTS DIAGNOSED (%) | 70% | 70% | 70% | 70% | 70% | 70% | 70% | 70% | 70% | 70% | 70% |
| PATIENTS DIAGNOSED (MN) | 2.5 | 2.5 | 2.6 | 2.6 | 2.7 | 2.8 | 2.8 | 2.9 | 2.9 | 3.0 | 3.0 |
| PATIENTS TREATED WITH LEVODOPA (%) | 60% | 60% | 60% | 60% | 60% | 60% | 60% | 60% | 60% | 60% | 60% |
| NUMBER OF PATIENTS TREATED (MN) | 1.5 | 1.5 | 1.6 | 1.6 | 1.6 | 1.7 | 1.7 | 1.7 | 1.8 | 1.8 | 1.8 |
| MID TO LATE STAGE PATIENTS (%) | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% |
| NUMBER OF MID TO LATE STAGE PATIENTS (MN) | 1.2 | 1.2 | 1.2 | 1.3 | 1.3 | 1.3 | 1.3 | 1.4 | 1.4 | 1.4 | 1.5 |
| MID TO LATE STAGE PATIENTS WITH PD-LID (%) | 40% | 40% | 40% | 40% | 40% | 40% | 40% | 40% | 40% | 40% | 40% |
| NUMBER OF PATIENTS WITH PD-LID | 478'588 | 488'160 | 497'923 | 507'882 | 518'039 | 528'400 | 538'968 | 549'748 | 560'743 | 571'957 | 583'397 |
| PENETRATION (%) | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 2% | 8% |
| NUMBER OF PATIENTS | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 11'439 | 46'672 |
| COST OF THERAPY PER YEAR (CHF) | 10'000 | 10'000 | 10'000 | 10'000 | 10'000 | 10'000 | 10'000 | 10'000 | 10'000 | 10'000 | 10'000 |
| PATIENT COMPLIANCE (%) | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% |
| **SALES (CHF MN)** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **92** | **373** |
| CHANGE (%) | | | | | | | | | | | 308% |
| ROYALTY (%) | 10% | 10% | 10% | 10% | 10% | 10% | 10% | 10% | 10% | 10% | 10% |
| ROYALTIES (CHF MN) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 9 | 37 |
| UPFRONT & MILESTONE PAYMENTS (CHF MN) | 0 | 0 | 0 | 10 | 0 | 0 | 0 | 25 | 0 | 15 | 0 |
| **PROFIT BEFORE TAX (CHF MN)** | **0** | **0** | **0** | **10** | **0** | **0** | **0** | **25** | **0** | **24** | **37** |
| TAX RATE (%) | 0% | 0% | 0% | 0% | 0% | 0% | 5% | 10% | 15% | 20% | 20% |
| TAXES (CHF MN) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | -3 | 0 | -5 | -7 |
| **PROFIT (CHF MN)** | **0** | **0** | **0** | **10** | **0** | **0** | **0** | **23** | **0** | **19** | **30** |

| **UNITED STATES** | **2017E** | **2018E** | **2019E** | **2020E** | **2021E** | **2022E** | **2023E** | **2024E** | **2025E** | **2026E** | **2027E** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| NUMBER OF PATIENTS | 1.1 | 1.2 | 1.2 | 1.2 | 1.2 | 1.3 | 1.3 | 1.3 | 1.3 | 1.4 | 1.4 |
| GROWTH (%) | 2% | 2% | 2% | 2% | 2% | 2% | 2% | 2% | 2% | 2% | 2% |
| PATIENTS DIAGNOSED (%) | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% |
| NUMBER OF PATIENTS DIAGNOSED (MN) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| PATIENTS TREATED WITH LEVODOPA (%) | 60% | 60% | 60% | 60% | 60% | 60% | 60% | 60% | 60% | 60% | 60% |
| NUMBER OF PATIENTS TREATED | 551'369 | 562'397 | 573'644 | 585'117 | 596'820 | 608'756 | 620'931 | 633'350 | 646'017 | 658'937 | 672'116 |
| MID TO LATE STAGE PATIENTS (%) | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% |
| NUMBER OF MID TO LATE STAGE PATIENTS | 441'095 | 449'917 | 458'916 | 468'094 | 477'456 | 487'005 | 496'745 | 506'680 | 516'813 | 527'150 | 537'693 |
| MID TO LATE STAGE PATIENTS WITH PD-LID (%) | 40% | 40% | 40% | 40% | 40% | 40% | 40% | 40% | 40% | 40% | 40% |
| NUMBER OF PATIENTS WITH PD-LID | 176'438 | 179'967 | 183'566 | 187'238 | 190'982 | 194'802 | 198'698 | 202'672 | 206'725 | 210'860 | 215'077 |
| PENETRATION (%) | 0% | 0% | 0% | 0% | 0% | 0% | 3% | 9% | 14% | 18% | 20% |
| NUMBER OF PATIENTS (MN) | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 4967.4 | 17227.1 | 27907.9 | 36900.5 | 41940.0 |
| COST OF THERAPY PER YEAR (CHF) | 24'564 | 24'564 | 24'564 | 24'564 | 24'564 | 24'564 | 24'564 | 24'564 | 24'564 | 24'564 | 24'564 |
| PATIENT COMPLIANCE (%) | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% |
| **SALES (CHF MN)** | **0** | **0** | **0** | **0** | **0** | **0** | **98** | **339** | **548** | **725** | **824** |
| CHANGE (%) | | | | | | | | 247% | 62% | 32% | 14% |
| ROYALTY (%) | 25% | 25% | 25% | 25% | 25% | 25% | 25% | 25% | 25% | 25% | 25% |
| ROYALTIES (CHF MN) | 0 | 0 | 0 | 0 | 0 | 0 | 24 | 85 | 137 | 181 | 206 |
| UPFRONT & MILESTONE PAYMENTS (CHF MN) | 0 | 0 | 0 | 0 | 25 | 10 | 15 | 0 | 50 | 0 | 80 |
| R&D COSTS (CHF MN) | 0 | -8 | -8 | -15 | -10 | -12 | -3 | 0 | 0 | 0 | 0 |
| **PROFIT BEFORE TAX (CHF MN)** | **0** | **-8** | **-8** | **-15** | **15** | **-2** | **37** | **85** | **187** | **181** | **206** |
| TAX RATE (%) | 0% | 0% | 0% | 0% | 0% | 0% | 5% | 10% | 15% | 20% | 20% |
| TAXES (CHF MN) | 0 | 0 | 0 | 0 | 0 | 0 | -2 | -8 | -28 | -36 | -41 |
| **PROFIT (CHF MN)** | **0** | **-8** | **-8** | **-15** | **15** | **-2** | **35** | **76** | **159** | **145** | **165** |

| | **2017E** | **2018E** | **2019E** | **2020E** | **2021E** | **2022E** | **2023E** | **2024E** | **2025E** | **2026E** | **2027E** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **GLOBAL SALES (CHF MN)** | **0** | **0** | **0** | **0** | **0** | **0** | **98** | **339** | **548** | **817** | **1'198** |
| CHANGE (%) | | | | | | | | 247% | 62% | 49% | 47% |
| **GLOBAL PROFIT (CHF MN)** | **0** | **-8** | **-8** | **-5** | **15** | **-2** | **35** | **99** | **159** | **164** | **195** |
| CHANGE (%) | | | 0% | -33% | -400% | -110% | -2437% | 181% | 61% | 3% | 18% |

| | | |
|---|---|---|
| WACC (%) | 7.0% | |
| **NPV TOTAL PROFIT (CHF MN)** | **980** | |
| NUMBER OF SHARES (MN) | 23.1 | |
| **NPV PER SHARE (CHF)** | **42.5** | |
| SUCCESS PROBABILITY | 20% | = PHASE IIA COMPLETED (PHASE III TO START IN H2 2018 DEPENDENT ON SUFFICIENT FUNDING/PARTNERING) |
| **RISK ADJUSTED NPV PER SHARE (CHF)** | **8.5** | |

### SENSITIVITY ANALYSIS

| | | **WACC (%)** | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | CHF/SHARE | 5.5 | 6.0 | 6.5 | 7.0 | 7.5 | 8.0 | 8.5 |
| | 55% | 28.5 | 26.7 | 25.0 | 23.4 | 21.9 | 20.5 | 19.2 |
| | 50% | 25.9 | 24.2 | 22.7 | 21.2 | 19.9 | 18.6 | 17.5 |
| | 45% | 23.3 | 21.8 | 20.4 | 19.1 | 17.9 | 16.8 | 15.7 |
| **SUCCESS PROBABILITY** | 40% | 20.7 | 19.4 | 18.1 | 17.0 | 15.9 | 14.9 | 14.0 |
| | 35% | 18.2 | 17.0 | 15.9 | 14.9 | 13.9 | 13.0 | 12.2 |
| | 30% | 15.6 | 14.5 | 13.6 | 12.7 | 11.9 | 11.2 | 10.5 |
| | 25% | 13.0 | 12.1 | 11.3 | 10.6 | 9.9 | 9.3 | 8.7 |
| | 20% | 10.4 | 9.7 | 9.1 | **8.5** | 8.0 | 7.4 | 7.0 |
| | 15% | 7.8 | 7.3 | 6.8 | 6.4 | 6.0 | 5.6 | 5.2 |

* MJFF = MICHAEL J. FOX FOUNDATION

ESTIMATES AS OF 8 JANUARY, 2018

SOURCE: VALUATIONLAB ESTIMATES

## DIPRAGLURANT-ER (MGLUR5 NAM) - FINANCIAL FORECASTS FOR NON-PARKINSONIAN DYSTONIA

| | |
|---|---|
| **INDICATION** | NON-PARKINSONIAN DYSTONIA |
| **DOSAGE** | ONCE OR TWICE DAILY 50-100 MG |
| **PRICE** | ANNUAL PRICE PER PATIENT: EU/ROW: CHF 10,000; US: USD 25,000 (CONSERVATIVE PRICING SIMILAR TO DIPRAGLURANT IR IN PD-LID) |
| **STANDARD OF CARE** | MUSCLE RELAXANTS (BACLOFEN), ANTICONVULSANTS (CLONAZEPAM, DIAZEPAM), BOTOX INJECTIONS OR DEEP BRAIN STIMULATION |
| **UNIQUE SELLING POINT** | EFFECTIVE THERAPY THAT TARGETS UNDERLYING MECHANISM (EXCESS GLUTAMATE RELEASE IN BRAIN CONTROLLING MOVEMENT) WITH GOOD TOLERABILITY |

### 7PS ANALYSIS

| | |
|---|---|
| **PATENT** | AT LEAST 2025 (COMPOSITION OF MATTER) EP1765795 GRANTED 2013; UP TO 2033 (EXTENDED RELEASE) WO2013186311 FILED 2013; UP TO 2034 (POLYMORPH PATENTS) |
| **PHASE** | PHASE IIA PROOF-OF-CONCEPT TRIAL TO START IN H1 2018 WITH RESULTS IN H1 2019 |
| **PATHWAY** | NON-PARKINSONIAN DYSTONIA IS AN ORPHAN DRUG INDICATION LEADING TO FASTER REVIEW TIMES |
| **PATIENT** | POTENTIAL REDUCTION OF AMOUNT AND SEVERITY OF MUSCLE CONTRACTIONS/SPASMS LEADS TO A SUBSTANTIAL IMPROVEMENT IN THE QUALITY OF LIFE FOR A PATIENT |
| **PHYSICIAN** | FIRST EFFECTIVE TREATMENT TO REDUCE THE AMOUNT AND SEVERITY OF MUSCLE CONTRACTIONS/SPASMS WITHOUT TOLERABITY ISSUES |
| **PAYER** | IMPROVEMENTS IN QUALITY OF LIFE AND LEAD TO A SUBSTANTIAL REDUCTION IN OVERALL TREATMENT COSTS SUCH AS OUTPATIENT CARE OR NURSING HOMES |
| **PARTNER** | WE ASSUME ADDEX TO PARTNER ON POSITIVE PIVOTAL TRIAL RESULTS IN 2022 |

### REVENUE MODEL

| **EUROPE / REST OF WORLD** | **2017E** | **2018E** | **2019E** | **2020E** | **2021E** | **2022E** | **2023E** | **2024E** | **2025E** | **2026E** | **2027E** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| NUMBER OF PATIENTS (MN) | 0.6 | 0.6 | 0.6 | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 | 0.8 |
| GROWTH (%) | 2% | 2% | 2% | 2% | 2% | 2% | 2% | 2% | 2% | 2% | 2% |
| PATIENTS DIAGNOSED (%) | 60% | 60% | 60% | 60% | 60% | 60% | 60% | 60% | 60% | 60% | 60% |
| PATIENTS DIAGNOSED (MN) | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.5 |
| PERCENTAGE TREATED (%) | 50% | 50% | 50% | 50% | 50% | 50% | 50% | 50% | 50% | 50% | 50% |
| PATIENTS TREATED (MN) | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| PENETRATION (%) | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 3% | 9% | 14% | 18% |
| NUMBER OF PATIENTS (MN) | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| COST OF THERAPY PER YEAR (CHF) | 10'000 | 10'000 | 10'000 | 10'000 | 10'000 | 10'000 | 10'000 | 10'000 | 10'000 | 10'000 | 10'000 |
| **SALES (CHF MN)** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **64** | **196** | **311** | **408** |
| CHANGE (%) | | | | | | | | | 206% | 59% | 31% |
| ROYALTY (%) | 25% | 25% | 25% | 25% | 25% | 25% | 25% | 25% | 25% | 25% | 25% |
| ROYALTIES (CHF MN) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 16 | 49 | 78 | 102 |
| UPFRONT & MILESTONE PAYMENTS (CHF MN) | 0 | 0 | 0 | 0 | 0 | 20 | 10 | 20 | 0 | 30 | 40 |
| R&D COSTS (CHF MN) | 0 | -3 | -6 | -8 | -8 | -8 | -4 | 0 | 0 | 0 | 0 |
| **PROFIT BEFORE TAX (CHF MN)** | **0** | **-3** | **-6** | **-8** | **-8** | **13** | **6** | **36** | **49** | **108** | **142** |
| TAX RATE (%) | 0% | 0% | 0% | 0% | 0% | 0% | 5% | 10% | 15% | 20% | 20% |
| TAXES (CHF MN) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | -4 | -7 | -22 | -28 |
| **PROFIT (CHF MN)** | **0** | **-3** | **-6** | **-8** | **-8** | **13** | **6** | **32** | **42** | **86** | **114** |

| **UNITED STATES** | **2017E** | **2018E** | **2019E** | **2020E** | **2021E** | **2022E** | **2023E** | **2024E** | **2025E** | **2026E** | **2027E** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| NUMBER OF PATIENTS (MN) | 0.3 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 |
| GROWTH (%) | 2% | 2% | 2% | 2% | 2% | 2% | 2% | 2% | 2% | 2% | 2% |
| PATIENTS DIAGNOSED (%) | 60% | 60% | 60% | 60% | 60% | 60% | 60% | 60% | 60% | 60% | 60% |
| PATIENTS DIAGNOSED (MN) | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.3 |
| PERCENTAGE TREATED (%) | 50% | 50% | 50% | 50% | 50% | 50% | 50% | 50% | 50% | 50% | 50% |
| PATIENTS TREATED (MN) | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| PENETRATION (%) | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 3% | 9% | 14% | 18% |
| NUMBER OF PATIENTS (MN) | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| COST OF THERAPY PER YEAR (CHF) | 24'564 | 24'564 | 24'564 | 24'564 | 24'564 | 24'564 | 24'564 | 24'564 | 24'564 | 24'564 | 24'564 |
| **SALES (CHF MN)** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **88** | **268** | **425** | **557** |
| CHANGE (%) | | | | | | | | | 206% | 59% | 31% |
| ROYALTY (%) | 25% | 25% | 25% | 25% | 25% | 25% | 25% | 25% | 25% | 25% | 25% |
| ROYALTIES (CHF MN) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 22 | 67 | 106 | 139 |
| UPFRONT & MILESTONE PAYMENTS (CHF MN) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 40 | 0 |
| **PROFIT BEFORE TAX (CHF MN)** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **22** | **67** | **116** | **139** |
| TAX RATE (%) | 0% | 0% | 0% | 0% | 0% | 0% | 5% | 10% | 15% | 20% | 20% |
| TAXES (CHF MN) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | -2 | -10 | -23 | -28 |
| **PROFIT (CHF MN)** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **20** | **57** | **93** | **111** |

| | **2017E** | **2018E** | **2019E** | **2020E** | **2021E** | **2022E** | **2023E** | **2024E** | **2025E** | **2026E** | **2027E** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **GLOBAL SALES (CHF MN)** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **152** | **464** | **736** | **965** |
| CHANGE (%) | | | | | | | | | 206% | 59% | 31% |
| **GLOBAL PROFIT (CHF MN)** | **0** | **-3** | **-6** | **-8** | **-8** | **13** | **6** | **52** | **99** | **179** | **225** |
| CHANGE (%) | | | 100% | 25% | 0% | -267% | -54% | 814% | 89% | 82% | 26% |

| | | |
|---|---|---|
| WACC (%) | 7.0% | |
| **NPV TOTAL PROFIT (CHF MN)** | **1'051** | |
| NUMBER OF SHARES (MN) | 23.1 | |
| **NPV PER SHARE (CHF)** | **45.5** | |
| SUCCESS PROBABILITY | 8% | = PHASE I COMPLETED (PHASE IIA POC TO START IN H1 2018 & FUNDED) |
| **RISK ADJUSTED NPV PER SHARE (CHF)** | **3.6** | |

### SENSITIVITY ANALYSIS

| | | **WACC (%)** | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | CHF/SHARE | 5.5 | 6.0 | 6.5 | 7.0 | 7.5 | 8.0 | 8.5 |
| | 50% | 27.2 | 25.6 | 24.1 | 22.8 | 21.5 | 20.3 | 19.2 |
| | 45% | 24.5 | 23.0 | 21.7 | 20.5 | 19.3 | 18.3 | 17.2 |
| | 40% | 21.7 | 20.5 | 19.3 | 18.2 | 17.2 | 16.2 | 15.3 |
| | 35% | 19.0 | 17.9 | 16.9 | 15.9 | 15.0 | 14.2 | 13.4 |
| **SUCCESS PROBABILITY** | 30% | 16.3 | 15.4 | 14.5 | 13.7 | 12.9 | 12.2 | 11.5 |
| | 25% | 13.6 | 12.8 | 12.1 | 11.4 | 10.7 | 10.1 | 9.6 |
| | 20% | 10.9 | 10.2 | 9.7 | 9.1 | 8.6 | 8.1 | 7.7 |
| | 15% | 8.2 | 7.7 | 7.2 | 6.8 | 6.4 | 6.1 | 5.7 |
| | 8% | 4.3 | 4.1 | 3.9 | **3.6** | 3.4 | 3.2 | 3.1 |

ESTIMATES AS OF 8 JANUARY, 2018

SOURCE: VALUATIONLAB ESTIMATES

# Unique Selling Point

With no effective treatment for Parkinson's disease levodopa-induced dyskinesia (PD-LID), dipraglurant IR has the potential to become first in class and one of the first drugs for this indication. Successful treatment of PD-LID could change the way Parkinson's disease is treated, enabling physicians to use levodopa, earlier and more aggressively.

# 7P's Analysis

**Patent:** A solid composition-of-matter patent protects dipraglurant IR until 2025. Assuming first launches in 2020, the drug has an effective patent life of at least 5 years. Additional patents covering polymorphs and formulations of dipraglurant could extend patent protection to 2032. Orphan drug market exclusivities could provide longer protection as well (7 years and 10 years from launch in the US and EU, respectively).

**Phase:** Addex has completed a phase IIa proof-of-concept study in levodopa-induced dyskinesia in Parkinson's disease. The company is preparing, in consultation with key opinion leaders, for a phase IIb/III study in PD-LID, scheduled to start in Q3 2016. The initiation of the study depends on securing sufficient funds through investors or a partner. The estimated probability of success at this stage of development is 15%.

**Pathway:** We believe the regulatory pathway in PD-LID is quite straightforward and similar to the proof-of-concept trial demonstrating a clinical benefit in reducing dyskinesia and "off-time", while improving "on-time". Approval should be attained with at least one positive pivotal phase III demonstrating a significant benefit in reducing levodopa-induced dyskinesia using the UDysRS score. Orphan drug designation could simplify the regulatory pathway potentially with less patients, lower costs and faster timelines.

**Patient:** With no effective treatment for PD-LID, dipraglurant IR has the potential to have a major change on the quality of life for patients with moderate to severe Parkinson's disease, by reducing debilitating dyskinesia without worsening Parkinson’s symptoms. Moreover, patients can postpone the need for outside help.

**Physician:** Dipraglurant IR can be added to mainstay levodopa therapy, thereby reducing one of the main side effects of levodopa being dyskinesia. Consequently, moderate PD patients can be given levodopa treatment earlier and more aggressively, and severe PD patients can be treated longer and more aggressively with levodopa.

**Payer:** The largest share of direct cost in Parkinson's disease comes from inpatient care and nursing homes, while the share from medication is substantially lower. Any delay in the progression of the disease or reduced debilitating side effects, in particular dyskinesia, has a substantial impact on total treatment costs. The average total treatment cost of a Parkinson’s patient in the US rises to USD 26,000 from USD 19,000 when PD-LID occurs.

**Partner:** The Michael J. Fox Foundation supported the phase IIa development with a USD 900,000 grant. With the support of an additional USD 1 mn grant Addex has prepared dipraglurant for the start of phase III trials in PD-LID, which are expected to start in H2 2018. The company plans to develop dipraglurant by itself with the help of grants and/or investments from investors. Addex continues to actively seek a development and commercialization partner to fully develop dipraglurant in its two main indications, PD-LID and non-Parkinsonian dystonia’s.

# Parkinson's Disease Market

Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease. Nevertheless, the Parkinson's disease market is relatively small in terms of sales at around USD 4 bn, reflecting the lack of new efficacious treatment introductions, with most drugs no longer patent protected. Major players included Novartis, Bristol-Myers Squibb and GlaxoSmithKline. Several smaller players have developed new formulations (extended/controlled-release, patches, orally disintegrating tablets) extending the patent life of some existing branded drugs. The combined direct (medication, inpatient care) and indirect cost (inability to work) of Parkinson's disease is estimated to be nearly USD 25 bn per year in the US alone.

| PARKINSON'S DISEASE - KEY FACTS | |
|---|---|
| MARKET SIZE | USD 4 BN |
| PREVALENCE | 7-10 MN GLOBALLY, 1 MN IN US, > 1 MN IN EU |
| INCIDENCE | 300,000 GLOBALLY, 100,000 IN US, >100,000 IN EU; 0.3% OF POPULATION |
| UNDERLYING CAUSE | - LOSS AND DEGENERATION OF DOPAMINERGIC NEURONS IN STRIATA NIGRA<br>- LOSS OF STRATIAL NEUROTRANSMITTER DOPAMINE |
| SYMPTOMS | - TREMOR (SHAKING OF HANDS, ARMS, LEGS, JAW, FACE)<br>- RIGIDITY (LIMBS, TRUNK)<br>- BRADYKINESIA (SLOWNESS OF MOVEMENT)<br>- POSTURAL INSTABILITY (POOR BALANCE AND COORDINATION) |
| DRUG CLASS (KEY BRANDS) | - LEVODOPA/CARBIDOPA (MADOPAR, SINEMET CR, PARCOPA, STALEVO, DUODOPA)<br>- DOPAMINE AGONIST (MIRAPEX, REQUIP, APOKYN, PARLODEL, NEUPRO PATCH)<br>- MAO-B INHIBITORS (AZILECT, ELDEPRYL, ZELAPAR ODT, XADAGO)<br>- COMT INHIBITORS (COMTAN, TASMAR)<br>- ANTICHOLINERGICS (COGENTIN, ARTANE)<br>- OTHER (SYMMETREL FOR DYSKINESIA, EXELON FOR DEMENTIA) |
| MAJOR PLAYERS (KEY BRANDS) | - NOVARTIS (STALEVO, PARLODEL, COMTAN)<br>- BRISTOL MYERS SQUIBB (SINEMET CR)<br>- GLAXOSMITHKLINE (REQUIP)<br>- TEVA (AZILECT)<br>- UCB (NEUPRO PATCH)<br>- BOEHRINGER INGELHEIM (MIRAPEX ER)<br>- US WORLDMEDS (APOKYN, XADAGO)<br>- VALEANT (ZELAPAR ODT, TASMAR)<br>- ABBVIE (DUODOPA)<br>- ENDO PHARMACEUTICALS (SYMMETREL)<br>- ZAMBON/MEIJI SEIKA (XADAGO) |

SOURCE: VALUATIONLAB, NIH, WHO, PARKINSONS.ORG, PDF.ORG, COMPANY REPORTS

Parkinson's disease affects an estimated 7-10 million people globally with about 1 million patients in the US and a similar amount in the EU, with significant prevalence growth expected due to an aging population. The disease is a slowly progressive degenerative disorder of the central nervous system that initially affects movement, and later cognition and behavior. Dementia commonly occurs in the advanced stage of disease. The mean age of onset is typically around 60 years (rare in people under the age of 40 years). In people taking medication (levodopa), the progression time of symptoms to a stage of high dependency from caregivers may range from 8 to 15 years.

**Three stages of severity are usually distinguished;**

1) **Early stage**, in which the patient has developed some disability and where drug treatment may be required (dopamine agonists, anticholinergics, MAO-B inhibitors)
2) **Mid stage**, where the symptoms can be rather severe and include the inability to walk straight or stand, with a noticeable slowing of movements (bradykinesia).
3) **Late or advanced stage**, in which an individual develops severe motor complications (dyskinesia) related to levodopa use. Most patients are unable to complete day-to-day tasks and usually cannot live on their own.

Early in the disease the most obvious symptoms are movement-related. These include tremor, rigidity, slowness of movement, and difficulty with walking and gait. The motor symptoms of the disease result from the death of dopamine-generating cells in the

substantia nigra, a small tract of neurons in the brain containing dopamine, which control voluntary movements. The cause of this cell death is still unknown.
The severity and progression of Parkinson's disease is measured using several rating scales such as the Hoehn and Yahr (focus on movement symptoms) or **UPDRS** (United Parkinson's Disease Rating Scale - more comprehensive than Hoehn and Yahr, taking into account cognitive difficulties, daily activities and treatment complications).

**Current drug treatment aims to delay symptoms and use of levodopa**
Because there is no cure for Parkinson's disease, the primary aim of treatment is to relieve symptoms and keep the patient functional as long as possible. Current treatments are effective at managing the early motor symptoms, mainly through the use of (generic) levodopa and dopamine agonists. Mainstay treatment is levodopa, an oral precursor of the neurotransmitter dopamine. It is well established as the most effective treatment for Parkinson's disease for over 30 years, with most patients noticing an immediate improvement. However, as the disease progresses and dopamine generating cells continue to be lost, these drugs eventually become ineffective at treating the symptoms and at the same time produce **dyskinesia**, a complication marked by involuntary jerking and twisting movements. Other treatment related complications include end-of-dose deterioration, unpredictable "on/off" motor fluctuations, hypotension, nausea, anorexia and psychiatric effects. These problems have led to the development of strategies that aim to limit or delay the onset of levodopa-related complications and have become the key drivers for the Parkinson's disease market with the introduction of dopamine agonists, MOA-B and COMT inhibitors. Dopamine agonists and MAO-B inhibitors are primarily used as mono-therapy in the early stages of the disease to delay the use of levodopa. **Dopamine agonists** work by directly stimulating the dopamine receptors to bypass degenerating brain cells. **MOA-B inhibitors** block a key enzyme that is responsible for the breakdown of dopamine. **COMT-inhibitors** block an enzyme responsible for the breakdown of levodopa in the body, thereby increasing the amount of levodopa available to reach the brain. Consequently COMT inhibitors are prescribed together with levodopa. When drug treatment is no longer sufficient to control symptoms, lesional surgery or deep brain stimulation (DBS), through implantation of a so-called brain pacemaker can be of use. In the final stages of disease, palliative care is provided to enhance quality of life.

**New market entrants expected to spark growth**
The introduction of new drugs, improved formulations of existing drugs, and the ageing of the population (higher prevalence) should drive growth in the Parkinson’s disease market.

**Improved formulations of existing drugs, including:** Abbvie's **Duodopa**, a carbidopa/levodopa intestinal gel (approved, Impax’s **Rytary**, an extended-release capsule formulation of carbidopa/levodopa (approved), and NeuroDerm's **ND0611/0612**, a carbidopa/levodopa subcutaneous patch pump (phase II), and Mylan’s/US WorldMeds’ Apokyn, a non-ergoline dopamine agonist for the treatment of acute hypomobility.

**New molecules and novel approaches, including:** Newron/Zambon's **Xadago** (approved in EU & US) a dual mechanism of action drug that provides both MAO-B and glutamate inhibition, adenosine 2a (A2a) agonists such as Kyowa-Kirin's **istradefylline** (global phase III did not meet primary endpoint, Japan approved as Nouriast) Adamas Pharmaceutical’s **Gocovri** a controlled-release formulation of amantadine controlled-release 1st approved PD-LID treatment in the US), and Addex's **dipraglurant** (phase II), which targets metabotropic glutamate receptor 5 (mGluR5).

# Pipeline – ADX71441 another blockbuster opportunity

Only dipraglurant IR (PD-LID) and dipraglurant ER (dystonia) are in our current valuation, as the other pipeline projects have no validated proof-of-concept, yet, including ADX71441 ($GABA_B$ PAM) for addiction. Revised plans for the key pipeline projects have been drafted with key opinion leaders (KOL's) and therapeutic area focused KOL advisory panels have been put in place. Progression of each project leads to a substantial increase in value and a higher probability of approval and partnering.

**Strategic partnership with Indivior for ADX71441 highlights pipeline potential**

In January 2017, Addex signed a strategic partnership with Indivior to accelerate the development of ADX71441 ($GABA_B$ PAM) for addiction in return for a USD 5 mn upfront payment and potential milestones of USD 330 mn and tiered royalties up to double digit. Addex will receive USD 4 mn of guaranteed research funding over 2 years and retains rights to advance additional $GABA_B$ PAM's in CMT1A neuropathy. Indivior is a global specialty pharmaceutical company, headquartered in Richmond, Virginia, USA, with more than 900 employees globally. The company is the world leader in opioid addiction treatments, such as Subutex (buprenorphine), with group sales amounting to USD 1 bn in 2016. In our view, the strategic partnership with Indivior highlights Addex' pipeline potential, where ADX71441, with a unique profile in addiction, complements Indivior's pipeline and strategic focus.

**Increasing evidence $GABA_B$ receptor is involved in addiction**

There is increasing evidence that activating the $GABA_B$ receptor plays an important role in addiction such as cocaine, alcohol and nicotine. GABA is the major inhibitory neurotransmitter in the brain and is implicated in the modulation of central reward processes. Administration of $GABA_B$ receptor agonists or $GABA_B$ PAMs (positive allosteric modulators) decreased self-administration of various drugs of abuse.

**Early evidence of conventional $GABA_B$ receptor agonists in addiction…**

$GABA_B$ receptor agonists such as baclofen inhibited cue-induced reinstatement of nicotine and cocaine-seeking behavior in rodents. These animal behavioral models are used to create a disease model of drug addiction that resembles human addiction behavior. Animals are conditioned to perform one action, typically a lever press, in order to receive a drug. The effect of the treatment can be measured by the reduction of the lever press. The use of baclofen has also proven efficiency in craving, drinking and anxiety reduction, thereby promoting abstinence. Similar effects on addiction were seen in animal behavior models with other conventional $GABA_B$ receptor agonists, such as the scientific research compounds CGP44532 (reduces cocaine reinforcement, decreased nicotine self-administration in the rat), and SKF-97541 (reduces cocaine sensitization in the rat).

**… as well as with $GABA_B$ PAMs**

There is even growing early evidence that $GABA_B$ PAMs have an effect on addiction in animal behavior models. The scientific research compound CGP7930 demonstrated reduced self-administration of ethanol and cocaine and had anxiolytic effects in animal studies. BHF-177, a new GS39783 analogue (which is limited to research purposes only due to genotoxicity, which may cause cancer) has shown to reduce self-administration of nicotine in animal models and does not induce genotoxicity as seen with GS39783. And finally, Addex' own commercial compound ADX71441 ($GABA_B$ PAM) demonstrated early efficacy in several animal models in alcohol consumption and nicotine withdrawal.

**PAMs may have an edge over conventional $GABA_B$ receptor agonists**

As a result, compounds that activate the GABAB receptor could provide new pharmaceutical treatment options for various addictions. Baclofen, which has been long on the market as a muscle relaxant, is now being developed for treating alcoholism using high doses. However, broad use of baclofen was limited due to its unfavorable side effect profile, which includes sedation, tolerance, cognitive disruption and withdrawal syndrome (e.g. hallucinations, delusions, confusion, agitation and delirium), in particular in chronic use at high doses.

ADX71441 ($GABA_B$ PAM), being a positive allosteric modulator, appears to have an important edge over baclofen with a differentiated tolerability and pharmacokinetic profile. No sign of tolerance development on efficacy has been seen after repeated dosing while initial central nervous system related side effects diminish and disappear after repeated dosing. Furthermore, the long half-life of ADX71441 ($GABA_B$ PAM) bodes for convenient once daily dosing, increasing patient compliance.

**Healthcare agencies worldwide actively spur research in addiction**

Currently, there are no effective and well-tolerated prescription drugs for alcoholism or nicotine addiction. The World Health Organization estimates that about 140 million people throughout the world suffer from alcohol dependence. This leads to a lot of harm to the individuals, their families and society. Excessive alcohol consumption damages almost every organ in the body and the cumulative toxic effects can cause both medical (cirrhosis of the liver, pancreatitis, heart disease, peptic ulcers, sexual dysfunction) and psychiatric (epilepsy, dementia, psychosis, anxiety & depression) problems. Excessive alcohol consumption is estimated to cost USD 223 bn per year in the US alone.

Smoking is the leading preventable cause of death in many countries. It is estimated that each year one in every five deaths in the US is the result of smoking. Economically, more than USD 96 bn of total US healthcare costs each year are attributable directly to smoking. Nicotine is the primary reinforcing component of tobacco that leads to addiction. Cigarette smoking harms nearly every organ in the body, and can lead to lung, mouth, throat, esophagus, stomach, pancreas, cervix, kidney and bladder cancer, as well as acute myeloid leukemia, and chronic obstructive pulmonary disease (COPD).

An effective and well-tolerated therapy that addresses alcohol or nicotine addiction addresses a significant unmet medical need. No wonder that many healthcare agencies across the world stimulate research in this area, through partnerships, providing scientific and research resources and financial grants.

**Two partnerships with leading organizations of the NIH**

Addex has established important partnerships with two organizations of the US NIH (National Institutes of Health) to explore the use ADX71441 ($GABA_B$ PAM) in addiction and drug abuse.

1. **NIDA collaboration for nicotine and cocaine addiction**
   At the end 2013 Addex announced a partnership with the NIDA (National Institute on Drug Abuse) to evaluate the pharmacology of ADX71441 ($GABA_B$ PAM) and ADX88178, an mGlu4 PAM in preclinical models of drug abuse and addiction. The collaboration will evaluate Addex drug candidates, ADX71441 ($GABA_B$ PAM) and ADX88178 in a battery of preclinical models to study their potential as treatments for nicotine and cocaine addiction. In October 2017, he NIDA awarded a USD 5.3

mn grant to support clinical trials of ADX71441 for the treatment of cocaine use disorders.

2. **NIAAA collaboration for alcohol use disorder**
   In January 2015 Addex entered a collaboration with the NIAAA (National Institute on Alcohol Abuse and Alcoholism to evaluate the pharmacology of ADX71441 ($GABA_B$ PAM), in preclinical models of alcohol use disorder. The collaboration successfully evaluated ADX71441 ($GABA_B$ PAM) in a battery of preclinical models of alcohol use disorder, which substantially increases the probability of ongoing support of the NIAAA to develop the compound in this indication with a high unmet medical need.

**Peak sales of CHF 1 bn in addiction with phase I safety trials to start in H2 2018 (NOT included in valuation)**

Needless to say, an effective and well-tolerated drug for alcohol abuse or nicotine addiction addresses a blockbuster market potential. Pfizer's smoking cessation drug Chantix (varenicline) generated USD 846 mn in 2008, only two years after launch. A black box warning for the risk of suicide in 2009 led to a decline in sales. Nevertheless, the drug continues to generate sales of more than USD 500 mn per year. There is an even larger need for effective prescription drugs for treating alcoholism. Sales of leading drugs such as Merck KGaA's Campral (acamprosate) disappointed, not topping annual sales of USD 100 mn. In practice patient response rates are relatively modest and not always consistent, while tolerability issues have hampered broad uptake. Therefore, we believe peak sales for ADX71441 ($GABA_B$ PAM) could easily amount to CHF 1+ bn, if developed successfully in just one of the targeted indications. Indivior plans to start phase I safety trials in H2 2018 and expects first launches to occur in 2024. Given the early stage of development, the lack of proof-of-concept in humans, and uncertainty which indication Addex will pursue, we have excluded any sales forecasts for ADX71441 ($GABA_B$ PAM) in our valuation.

# Income Statement

## ADDEX THERAPEUTICS

SHARE PRICE (CHF) 3.65

| INCOME STATEMENT (CHF MN) | 2016 | 2017E | 2018E | 2019E | 2020E | 2021E | 2022E | 2023E | 2024E | 2025E | 2026E |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **PRODUCT SALES (INCL. PARTNER SALES)** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **98** | **490** | **1'244** | **2'180** |
| CHANGE (%) | | | | | | | | | 402% | 154% | 75% |
| **ROYALTIES** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **24** | **123** | **280** | **448** |
| CHANGE (%) | | | | | | | | | 402% | 128% | 60% |
| **UPFRONT & MILESTONE PAYMENTS** | **0** | **0** | **7** | **2** | **12** | **25** | **50** | **50** | **55** | **85** | **105** |
| CHANGE (%) | | | | -71% | 500% | 108% | 100% | 0% | 10% | 54% | 24% |
| **OTHER REVENUES** | **0.4** | **0.4** | **3.1** | **2.7** | **0.2** | **0.2** | **0.2** | **0.2** | **0.2** | **0.2** | **0.2** |
| CHANGE (%) | -48% | 6% | 607% | -14% | -92% | 0% | 0% | 0% | 0% | 0% | 0% |
| - RESEARCH GRANTS | 0.29 | 0.42 | 3.08 | 2.65 | 0.20 | 0.20 | 0.20 | 0.20 | 0.20 | 0.20 | 0.20 |
| - OTHER INCOME | 0.13 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 |
| **REVENUES (EXCL. PARTNER SALES)** | **0.4** | **0.4** | **10.1** | **4.7** | **12.2** | **25.2** | **50.2** | **74.6** | **177.7** | **364.9** | **553.6** |
| CHANGE (%) | -48% | 6% | 2207% | -54% | 162% | 106% | 99% | 49% | 138% | 105% | 52% |
| **COGS** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** |
| **GROSS PROFIT** | **0.4** | **0.4** | **10.1** | **4.7** | **12.2** | **25.2** | **50.2** | **74.6** | **177.7** | **364.9** | **553.6** |
| CHANGE (%) | -48% | 6% | 2207% | -54% | 162% | 106% | 99% | 49% | 138% | 105% | 52% |
| MARGIN (%) | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% |
| **R&D** | **-2.5** | **-2.0** | **-10.5** | **-13.5** | **-23.0** | **-18.0** | **-19.5** | **-7.0** | **-0.5** | **-0.5** | **-0.5** |
| CHANGE (%) | 38% | -19% | 425% | 29% | 70% | -22% | 8% | -64% | -93% | 0% | 0% |
| **S,G&A** | **-1.1** | **-1.2** | **-1.2** | **-1.2** | **-1.2** | **-1.2** | **-1.2** | **-1.2** | **-1.2** | **-1.2** | **-1.2** |
| CHANGE (%) | -63% | 11% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% |
| **OPERATING COSTS** | **-3.5** | **-3.2** | **-11.7** | **-14.7** | **-24.2** | **-19.2** | **-20.7** | **-8.2** | **-1.7** | **-1.7** | **-1.7** |
| CHANGE (%) | -24% | -10% | 266% | 26% | 65% | -21% | 8% | -60% | -79% | 0% | 0% |
| **EBIT** | **-3.1** | **-2.8** | **-1.6** | **-10.0** | **-12.0** | **6.0** | **29.5** | **66.4** | **176.0** | **363.2** | **551.9** |
| CHANGE (%) | -19% | -12% | -42% | 526% | 19% | -150% | 391% | 125% | 165% | 106% | 52% |
| MARGIN (%) | | | | | | | | | | | |
| **EBITDA** | **-3.1** | **-2.7** | **-1.6** | **-10.0** | **-11.9** | **6.1** | **29.7** | **66.6** | **176.3** | **363.6** | **552.5** |
| CHANGE (%) | -19% | -12% | -43% | 538% | 19% | -151% | 384% | 125% | 165% | 106% | 52% |
| MARGIN (%) | -754% | -624% | -15% | -214% | -97% | 24% | 59% | 89% | 99% | 100% | 100% |
| **D&A** | **0.0** | **0.0** | **0.0** | **0.1** | **0.1** | **0.1** | **0.2** | **0.2** | **0.3** | **0.4** | **0.6** |
| **NET FINANCIAL INCOME/(EXPENSES)** | **0.0** | **-0.1** | **-0.1** | **-0.1** | **-0.1** | **-0.1** | **-0.1** | **-0.1** | **-0.1** | **-0.1** | **-0.1** |
| **PROFIT/LOSS BEFORE TAXES** | **-3.1** | **-2.8** | **-1.7** | **-10.1** | **-12.1** | **5.9** | **29.4** | **66.3** | **176.0** | **363.1** | **551.8** |
| CHANGE (%) | -25% | -10% | -41% | 503% | 19% | -149% | 395% | 125% | 165% | 106% | 52% |
| MARGIN (%) | -765% | -647% | -17% | -217% | -99% | 24% | 59% | 89% | 99% | 100% | 100% |
| **TAXES** | **0.0** | **0.0** | **0.0** | **0.0** | **0.0** | **0.0** | **0.0** | **-3.4** | **-17.8** | **-54.7** | **-104.6** |
| TAX RATE (%) | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 5.1% | 10.1% | 15.1% | 19.0% |
| **NET PROFIT/LOSS** | **-3.1** | **-2.8** | **-1.7** | **-10.1** | **-12.1** | **5.9** | **29.4** | **63.0** | **158.2** | **308.4** | **447.2** |
| CHANGE (%) | -25% | -10% | -41% | 503% | 19% | -149% | 395% | 114% | 151% | 95% | 45% |
| MARGIN (%) | -765% | -647% | -17% | -217% | -99% | 24% | 59% | 84% | 89% | 85% | 81% |
| **NET PROFIT/LOSS (EXCLUDING MILESTONES)** | **-3.1** | **-2.8** | **-8.7** | **-12.1** | **-24.1** | **-19.1** | **-20.6** | **13.0** | **103.2** | **223.6** | **342.2** |
| MARGIN (%) | | | -86% | -259% | -197% | -76% | -41% | 17% | 58% | 61% | 62% |
| **EPS (CHF)** | **-0.28** | **-0.20** | **-0.11** | **-0.66** | **-0.78** | **0.39** | **1.91** | **4.09** | **10.28** | **20.05** | **29.06** |
| CHANGE (%) | -29% | -26% | -46% | 503% | 19% | -149% | 395% | 114% | 151% | 95% | 45% |

ESTIMATES AS OF 8 JANUARY, 2018

SOURCE: VALUATIONLAB ESTIMATES

NOTE: At the end of FY 2016 Addex Therapeutics had a total of CHF 115 mn unrecorded tax loss carried forward. Due to the uncertainties as to whether Addex Therapeutics can use these, we have excluded them from our forecasts.

# Ratios & Balance Sheet

## ADDEX THERAPEUTICS

SHARE PRICE (CHF) 3.65

| RATIOS | 2016 | 2017E | 2018E | 2019E | 2020E | 2021E | 2022E | 2023E | 2024E | 2025E | 2026E |
|---|---|---|---|---|---|---|---|---|---|---|---|
| P/E | | | -33.5x | -5.6x | -4.7x | 9.4x | 1.9x | 0.9x | 0.4x | 0.2x | 0.1x |
| P/S | | | 5.6x | 12.0x | 4.6x | 2.2x | 1.1x | 0.8x | 0.3x | 0.2x | 0.1x |
| P/NAV | | | 1.9x | 3.0x | 8.0x | 4.3x | 1.3x | 0.5x | 0.2x | 0.1x | 0.1x |
| EV/EBITDA | | | -31.6x | -5.0x | -4.2x | 8.1x | 1.7x | 0.7x | 0.3x | 0.1x | 0.1x |

| PER SHARE DATA (CHF) | 2016 | 2017E | 2018E | 2019E | 2020E | 2021E | 2022E | 2023E | 2024E | 2025E | 2026E |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **EARNINGS** | **-0.28** | **-0.20** | **-0.11** | **-0.66** | **-0.78** | **0.39** | **1.91** | **4.09** | **10.28** | **20.05** | **29.06** |
| CHANGE (%) | -29% | -26% | -46% | 503% | 19% | -149% | 395% | 114% | 151% | 95% | 45% |
| **CASH** | **0.12** | **0.13** | **1.96** | **1.31** | **0.53** | **0.93** | **2.85** | **6.96** | **17.26** | **37.33** | **66.43** |
| CHANGE (%) | -49% | 7% | 1379% | -33% | -59% | 74% | 208% | 144% | 148% | 116% | 78% |
| **DIVIDENDS** | **0.00** | **0.00** | **0.00** | **0.00** | **0.00** | **0.00** | **0.00** | **0.00** | **0.00** | **0.00** | **0.00** |
| PAYOUT RATIO (%) | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% |
| **NET ASSET VALUE** | **0.02** | **0.05** | **1.89** | **1.23** | **0.45** | **0.85** | **2.77** | **6.88** | **17.18** | **37.25** | **66.36** |
| CHANGE (%) | -88% | 145% | 3926% | -35% | -63% | 87% | 227% | 148% | 150% | 117% | 78% |

| BALANCE SHEET (CHF MN) | 2016 | 2017E | 2018E | 2019E | 2020E | 2021E | 2022E | 2023E | 2024E | 2025E | 2026E |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **NET LIQUID FUNDS** | **1.4** | **1.9** | **30.2** | **20.2** | **8.2** | **14.2** | **43.8** | **107.0** | **265.5** | **574.3** | **1'022.1** |
| **TOTAL ASSETS** | **1.7** | **2.1** | **30.5** | **20.4** | **8.5** | **14.5** | **44.1** | **107.3** | **265.8** | **574.6** | **1'022.4** |
| **TOTAL SHAREHOLDERS' EQUITY** | **0.2** | **0.7** | **29.0** | **19.0** | **7.0** | **13.0** | **42.6** | **105.8** | **264.3** | **573.1** | **1'020.9** |
| CHANGE (%) | -87% | 199% | 4342% | -35% | -63% | 87% | 227% | 148% | 150% | 117% | 78% |
| RETURN ON EQUITY (%) | -1441% | -434% | -6% | -53% | -172% | 46% | 69% | 59% | 60% | 54% | 44% |
| **TOTAL EQUITY** | **0.2** | **0.7** | **29.0** | **19.0** | **7.0** | **13.0** | **42.6** | **105.8** | **264.3** | **573.1** | **1'020.9** |
| **FINANCIAL DEBT** | **0.0** | **0.0** | **0.0** | **0.0** | **0.0** | **0.0** | **0.0** | **0.0** | **0.0** | **0.0** | **0.0** |
| **EMPLOYEES** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| CHANGE (%) | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% |

| CASH FLOW STATEMENT (CHF MN) | 2016 | 2017E | 2018E | 2019E | 2020E | 2021E | 2022E | 2023E | 2024E | 2025E | 2026E |
|---|---|---|---|---|---|---|---|---|---|---|---|
| NET PROFIT / (LOSS) | -3.1 | -2.8 | -1.7 | -10.1 | -12.1 | 5.9 | 29.4 | 63.0 | 158.2 | 308.4 | 447.2 |
| DEPRECIATION & AMORTIZATION | 0.0 | 0.0 | 0.0 | 0.1 | 0.1 | 0.1 | 0.2 | 0.2 | 0.3 | 0.4 | 0.6 |
| OTHER NON-CASH ITEMS | 0.4 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **NET CASH USED IN OPERATING ACTIVITIES** | **-2.7** | **-2.8** | **-1.6** | **-10.0** | **-12.0** | **6.1** | **29.6** | **63.2** | **158.5** | **308.8** | **447.8** |
| CASH FLOW FROM INVESTING ACTIVITIES | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **FREE CASH FLOW** | **-2.7** | **-2.8** | **-1.6** | **-10.0** | **-12.0** | **6.1** | **29.6** | **63.2** | **158.5** | **308.8** | **447.8** |
| CASH FLOW FROM FINANCING ACTIVITIES | 1.5 | 3.2 | 30.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **CHANGE IN LIQUID FUNDS** | **-1.2** | **0.4** | **28.4** | **-10.0** | **-12.0** | **6.1** | **29.6** | **63.2** | **158.5** | **308.8** | **447.8** |

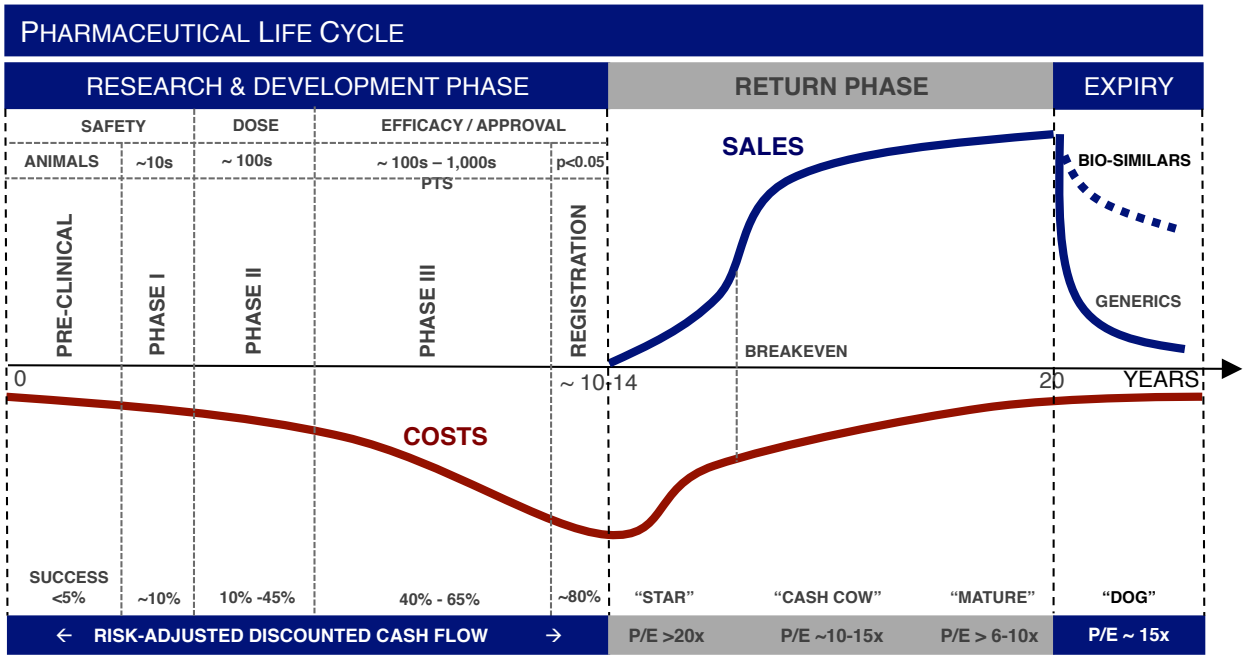
ESTIMATES AS OF 8 JANUARY, 2018

SOURCE: VALUATIONLAB ESTIMATES

# APPENDIX

## Pharmaceutical life cycle

To determine the value of a prescription (bio)pharmaceutical compound, it is critical to understand its life cycle. Fortunately, all compounds follow the same life cycle. The clock starts ticking after the compound is patented, providing 20 years of protection from generic competition. Market exclusivities can extend this protection period. The average Research & Development Phase takes 10-14 years, leading to an effective Return Phase of 6-10 years. The Development Phase has 3 distinct Phases, focused on safety (Phase I), dose (Phase II) and efficacy/clinical benefit (Phase III). The compound is filed for registration/approval at the FDA (US) or EMA (EU). The Return Phase is characterized by a star, cash cow, and mature phase. After patent expiry (or loss of market exclusivity) generic manufacturers may copycat the branded prescription drug, at significantly lower costs, leading to a sales and earnings implosion of the branded drug.




SOURCE: VALUATIONLAB

## Success probabilities & Royalties

In our risk-adjusted NPV calculations, we use standardized success probabilities based on historical clinical success rates. The success rate increases as the project progresses through development. Sales and earnings forecasts are based on the clinical and competitive profile of the compound. The more advanced the compound is, the more accurate the forecasts become as the target market can be defined. We conservatively exclude projects that lack Phase IIa proof-of-concept data in our valuations.

**SUCCESS PROBABILITIES & ROYALTIES**

| DEVELOPMENT STAGE | AIM | WHAT / WHO | SUCCESS PROBABILITY (%) | COSTS (USD MN) | ROYALTIES (%) |
|---|---|---|---|---|---|
| PRE-CLINICAL | SAFETY & PHARMACOLOGY DATA | LAB TESTS / ANIMALS - NO HUMANS! | < 5 | 3 | |
| PHASE I | SCREENING FOR SAFETY | HEALTHY VOLUNTEERS (10'S) | 5-15 | 3 | < 5 |
| PHASE IIA | PROOF-OF-CONCEPT | PATIENTS WITH DISEASE (10'S) | 10-20 | | |
| PHASE II | ESTABLISH THE TESTING PROTOCOL | PATIENTS WITH DISEASE (100'S) | 15-35 | 5 | 5-15 |
| PHASE IIB | OPTIMAL DOSAGE | PATIENTS WITH DISEASE (100'S) | 20-45 | 5-10 | |
| PHASE III | EVALUATE OVERALL BENEFIT/RISK | PATIENTS WITH DISEASE (1,000'S) | 40-65 | > 20-1,000 | 10-25 |
| REGULATORY FILING | DETERMINE PHYSICIAN LABELING | CLINICAL BENEFIT ASSESSMENT | 80-90 | | |
| APPROVAL | MARKETING AUTHORIZATION | PHYSICIANS FREE TO PRESCRIBE | 100 | | 15-30 |

SOURCE: VALUATIONLAB, TUFTS, FDA, EMA, CLINICALTRIALS.GOV

# Important Research Disclosures

valuationLAB AG is an independent life science research boutique with no securities or banking services. The company does not hold any positions in the securities mentioned in this report.

**Our financial analyses are based on the "Directives on the Independence of Financial Research" issued by the Swiss Bankers Association in January 2008.**

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## Risk Qualification

| | |
|---|---|
| Speculative | less than 1 year cash and breakeven beyond 1 year |
| High Risk | profitable within 2 years and 1 approved product/key indication (patent expiry > 5 years) |
| Medium Risk | profitable and/or sales from at least 2 marketed products/key indications (patent expiry > 5 years) |
| Low Risk | profitable and sales from >2 marketed products/key indications (patent expiry > 5 years) |

## Analyst Certification

The research analyst(s) identified on the first page of this research report hereby attest that all of the views expressed in this report accurately reflect their personal views about any and all of the subject securities or issuers. In order to ensure the independence of our research analysts, and their immediate household, are expressly prohibited from owning any securities in the valuationLAB AG research universe, which belong to their sector(s). Neither the research analyst nor his/her immediate household serves as an Officer, Director or Advisory Board Member of Addex Therapeutics Ltd.



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