PledPharma

Company presentation
November, 2019

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PledPharma

PledPharma is an **innovative**, **unique** and **integrated** pharmaceutical drug development company, focusing on improving treatments for diseases with substantial unmet medical need.

The company's most advanced project PledOx® is being developed to reduce nerve damage associated with chemotherapy. A global phase III program is ongoing.

The drug candidate Aladote® is being developed to reduce the risk of acute liver injury associated with acetaminophen poisoning. A proof of principle study has successfully been completed and will serve as the basis for the continued development.

Founded:	Listed:	Cash position[2]:
2006	Nasdaq First North	SEK 287m
Location:	**Market cap[1]:**	**FTE**
Stockholm	SEK ~1bn	9

Note: (**1**) Market capitalization as 30 Oct 2019. (2) Q3 2019 report

KEY LEADERSHIP MEMBERS

Nicklas Westerholm
CEO

Took office in June 2017 and has previously worked in the AstraZeneca Group since 1996 in number of global leadership roles in various business areas such as R&D, Finance & Investor Relations, and Commercial Manufacturing and Supply, most recently as VP in Project & Portfolio Management, Cardiovascular and Metabolic Diseases, R&D. Prior, Nicklas has held positions such as Executive Officer & VP Japan Operations and Director of Investor Relations. He has studied Analytical and Organic Chemistry at Stockholm University, Chemical Engineering at KTH and conducted studies at University of Warwick, INSEAD and Harvard Business School.

Yilmaz Mahshid, Ph.D.
CFO

Mr Mahshid has a Ph.D. from department of Medical Biochemistry and Biophysics at Karolinska Institute and has previously been employed at Industrifonden as an Investment Manager & Controller. He also has previous experience as a healthcare analyst at Pareto Securities. He started his career as a researcher at Karolinska Institutet and later at the pharmaceutical companies Biolipox and Orexo

Stefan Carlsson, MD, Ph.D.
CMO

Dr. Carlsson has a medical degree from Gothenburg University, where he also has a doctorate in physiology. Prior to joining PledPharma in 2017, he held a position at AstraZeneca as clinically responsible globally for several products in the market and in late stage development including Crestor® and Epanova®. He has a long experience from leading positions in preclinical and clinical drug development and has published thirty scientific articles in the fields of pharmacology and physiology.

Christian Sonesson, Ph.D.
VP Product Strategy & Development

Christian Sonesson was appointed VP Product Strategy & Development in 2017 following 13 years at Astra Zeneca. He has broad experience within drug development, including successfully leading products during Phase 3 (FORXIGA® in type 1 diabetes) and of regulatory submissions and defense, bringing new drug candidates to market in different regions. Christian has a Ph.D. in Biostatistics from Gothenburg University and an Executive MBA from Stockholm School of Economics.

Jacques Näsström, Ph.D.
CSO

Jacques was PledPharma's CEO prior to Westerholm joining PledPharma in 2011. More than 30 years of experience within the life science space with positions at Q-Med AB and AstraZeneca amongst others. He is a pharmacist with a Ph.D. in Pharmacology from Uppsala University and an MBA from Stockholm School of Economics.

Company history

2006

PledPharma AB is founded

2007-2010

Results from the MANFOL study

•••

Swedish Medical Products Agency (SMPA) approves PledPharma's application on clinical study on patients with acute heart infarct

•••

Submission of patent application for anticancer internationally

•••

License patent for use of PLED-pharmaceuticals

2011-2013

FDA approves the PLIANT-study

•••

Anti-cancer patent is approved in the US

•••

Results from the MANAMI-study

•••

PLIANT-study is approved by SMPA and international patent application for calmangafodipir is submitted

•••

PledOx®/calmangafodipir is discovered

•••

Lists on Nasdaq First North

2013-2016

Results from the PLIANT-study is presented at ASCO

•••

Monitoring data from the PLIANT-study indicates that PledOx® do not have a negative impact on cancer treatments

•••

Top line results from the PLIANT-study shows PledOx® reduces nerve damage in chemotherapy

•••

A new project on paracetamol overdose is presented (Aladote®)

•••

The PLIANT-study is fully recruited

2017

Proof-of-concept study of Aladote® in patients with paracetamol poisoning

•••

The Japanese company Solasia Pharma K.K. has undertaken to pay up to USD 83m to develop and commercialize PledOx®

•••

Results from the Phase II PLIANT-study was published and led PledPharma to initiate a global Phase III program. The program includes two double blinded placebo studies (POLAR-A & POLAR-M)

•••

Global Phase III program approved for PledOx® by EMA & FDA

2018-2019

Global Phase III program for PledOx® initiated

•••

PledPharma shares approved for trading on the main market of Nasdaq Stockholm

•••

PMDA supports expansion of the Phase III program for PledOx®

•••

EMA approved PledPharma's waiver application for the PIP

•••

Positive results from the Aladote® proof-of-principle study, drug was concluded safe, tolerable and with signals of reduced liver injury

•••

Results from the SUNCIST Phase I study shows that PledOx® have favourable safety profile

•••

Aladote® granted ODD

Executive summary

PledOx®

Prevents nerve damage caused by chemotherapy treatment in colorectal cancer patients

Phase III

- Huge unmet medical need with **No** approved drug for prevention or treatment of Chemotherapy Induced Peripheral Neuropathy (CIPN)
- Patient recruitment to the global phase III studies in US, EU and Asia is ongoing
- License agreement with Solasia to develop and commercialize PledOx® in Asia territory
- Top-line results expected before year-end 2020
- Indication expansion initiated - CIPN associated with taxanes

Aladote®

Prevents acute liver injury caused by paracetamol (acetaminophen) poisoning

Phase II

- Paracetamol (acetaminophen) poisoning is one of the most common sorts of overdoses
- No adequate treatment for high risk patients
- Successful results from a Phase Ib/IIa study in paracetamol overdosed patients – results presented at Annual Meeting of the Society of Toxicology, EASL ILC and Lancet EBiomedicine during 2019
- Orphan Drug Designation granted in 2019 in the US
- Design of next study finalised - subject to regulatory interactions in Q4 2019

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Neuropathy is associated with standard treatment of Colorectal Cancer (CRC) patients …. the 3rd most diagnosed cancer

Numbness and Tingling

Burning pain

Cold sensitivity during oxaliplatin treatment

Problems with sensation

Impacts balance with risk of falling

Challenge to use computer and keyboard

Difficulty in buttoning buttons

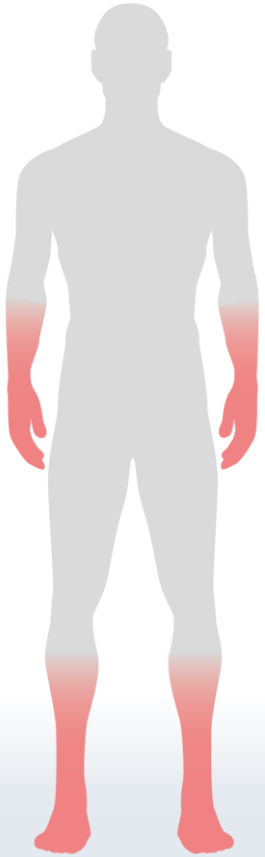
Depression

Anxiety

Severe insomnia

Reduced quality of life

Loss of ability to work



Oxaliplatin is associated with dose limiting and debilitating toxicities

40-60 % of patients get peripheral neuropathy during and up to 3 months after chemotherapy

20-30% of patients with symptoms >7 years post chemotherapy

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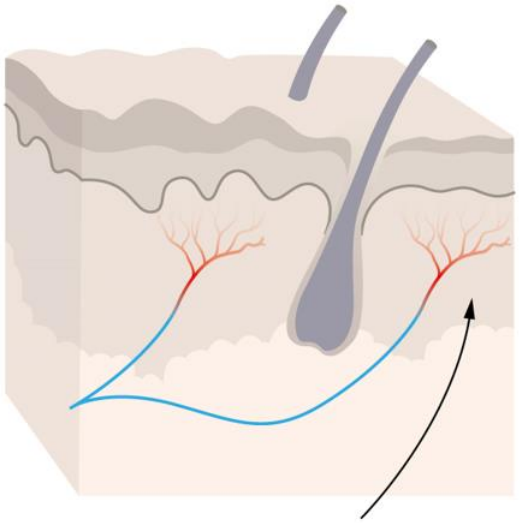
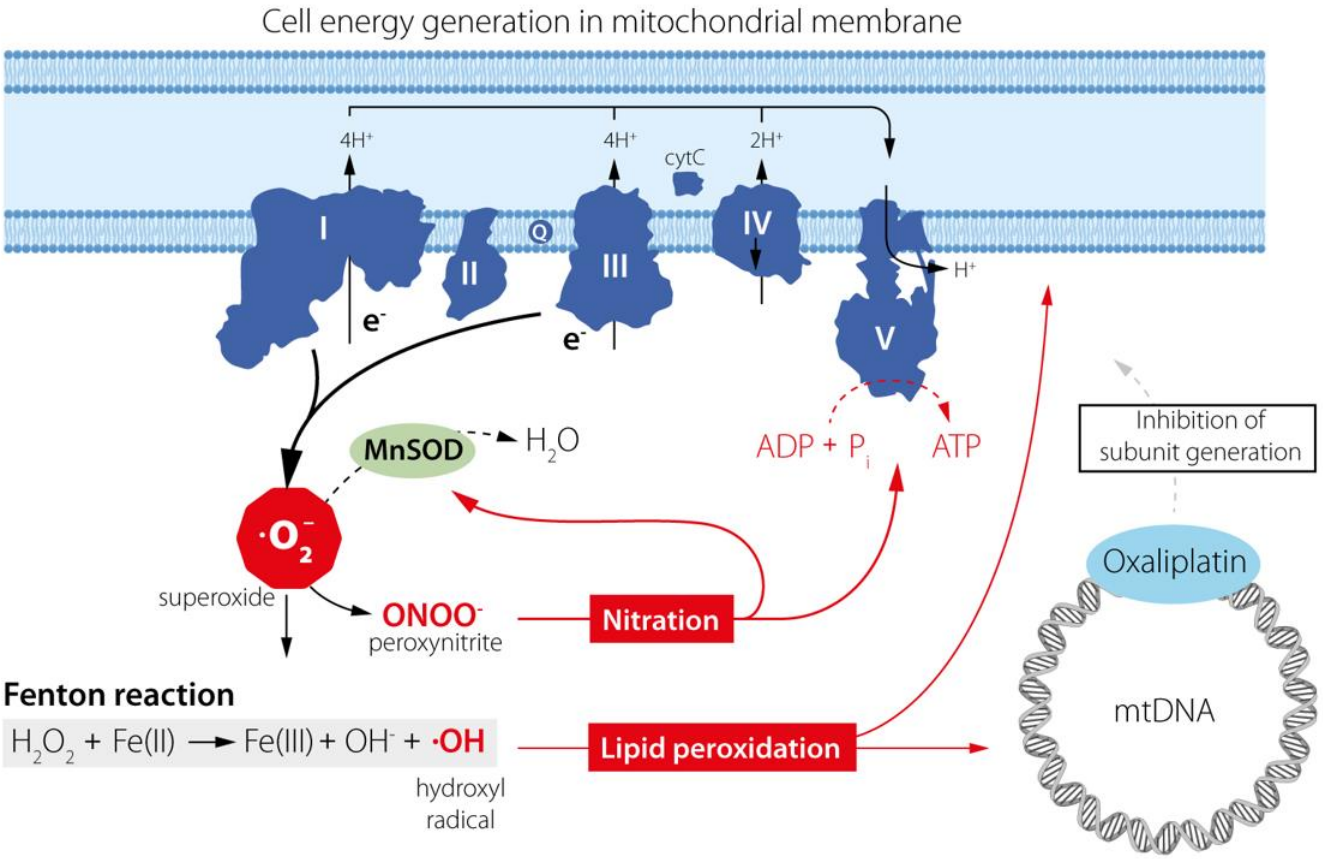
Chemotherapy treatment leads to mitochondrial dysfunction and CIPN

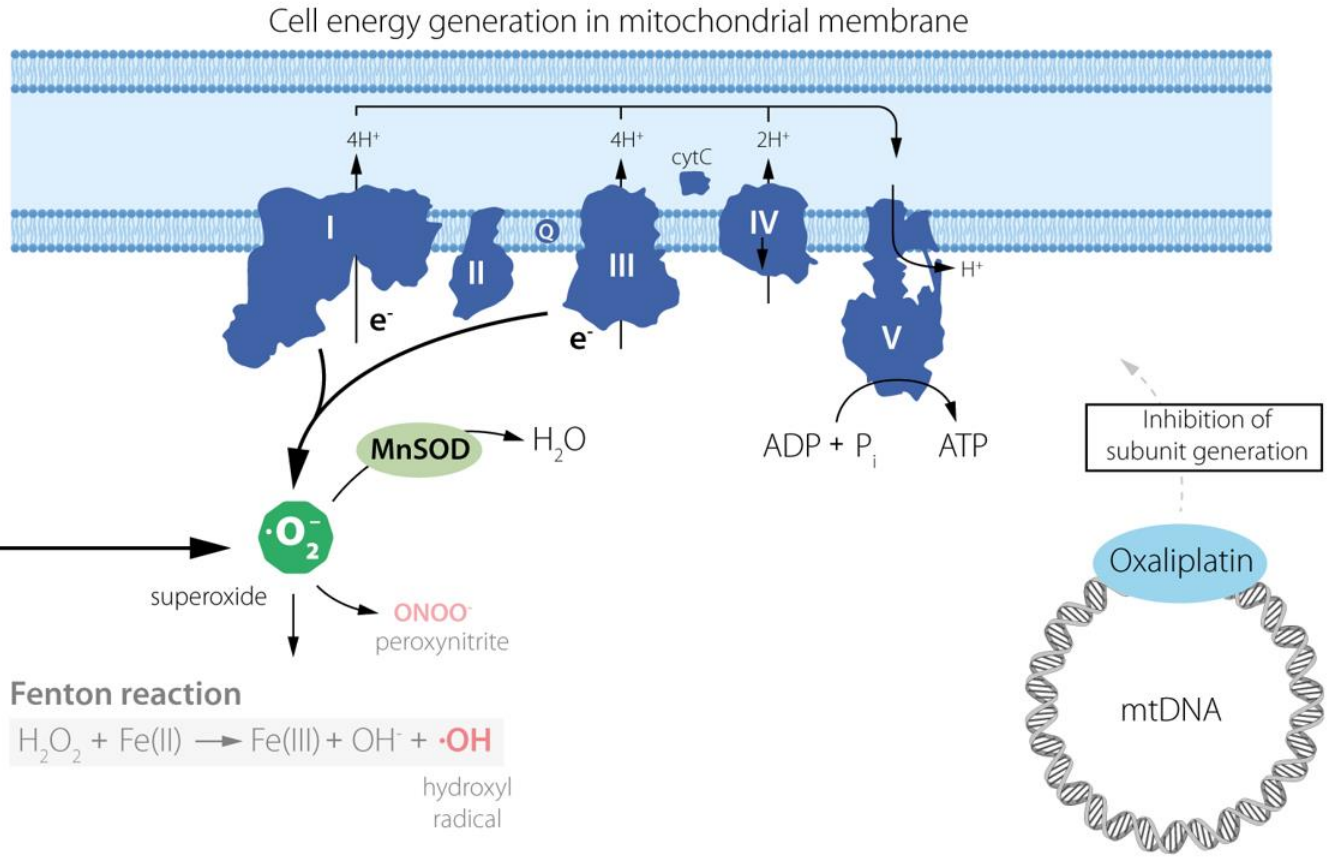


Nerve ending degeneration, due to lack of energy generated in mitochondria, leads to chronic CIPN



- Oxaliplatin binds to mtDNA, leading to inefficient energy generation and more superoxide
- MnSOD is an enzyme catalysing the degradation of superoxide

PledOx® prevents mitochondrial dysfunction



- Being a MnSOD mimetic, PledOx® supports superoxide regulation

- PledOx® binds free iron, inhibiting the Fenton reaction and thus lipid peroxidation

No approved drug for prevention or treatment of Chemotherapy Induced Peripheral Neuropathy

PledOx®

aims to become new standard of care

Prevention of chemotherapy induced peripheral neuropathy…

… without negative impact on the efficacy of chemotherapy

PledOx®

Chemotherapy

Easy to administrate
as pre-treatment to chemotherapy

Scientific rationale and results in Phase IIb study (PLIANT) provide reasons to believe in positive Phase III

PledOx®

The human body's own enzymatic defense against mitochondrial dysfunction

173 patients with metastatic CRC treated with PledOx® or placebo together with chemotherapy FOLFOX (oxaliplatin)

38% effect[1] on **investigator reported** CIPN symptoms (p=0.16 n.s)

77% effect[2] on **patient reported** CIPN symptoms (exploratory analysis; p=0.014)

No apparent negative effect on the efficacy of the chemotherapy treatment

Well tolerated

Note: (**1**) For investigator reported CIPN, an estimated odds ratio of 0.62 was reported on the primary endpoint, (**2**) For patient reported CIPN, an estimated odds ratio of 0.23 was reported on an exploratory endpoint similar to the forthcoming primary endpoint in the POLAR studies

PledOx® Global Phase III program

Two double-blind, randomised, placebo controlled studies

- POLAR-M (Metastatic CRC): 420 patients in US, EU and Asia undergoing chemotherapy (FOLFOX). PledOx® with the doses 2 µmol/kg respective 5 µmol/kg vs placebo.
- POLAR-A (Adjuvant CRC): 280 patients in EU and Asia undergoing chemotherapy (FOLFOX). PledOx® with the dose 5 µmol/kg vs placebo.
- Two complementary studies: POLAR-A provides CIPN evaluation in a homogenous population. POLAR-M is central to confirm that PledOx® has no detrimental effect on chemotherapy.

Primary endpoint

- Based on patient reported symptoms using the validated FACT/GOG-Ntx[1] instrument
- Assessed 9 months after first dose of chemotherapy

Survival data

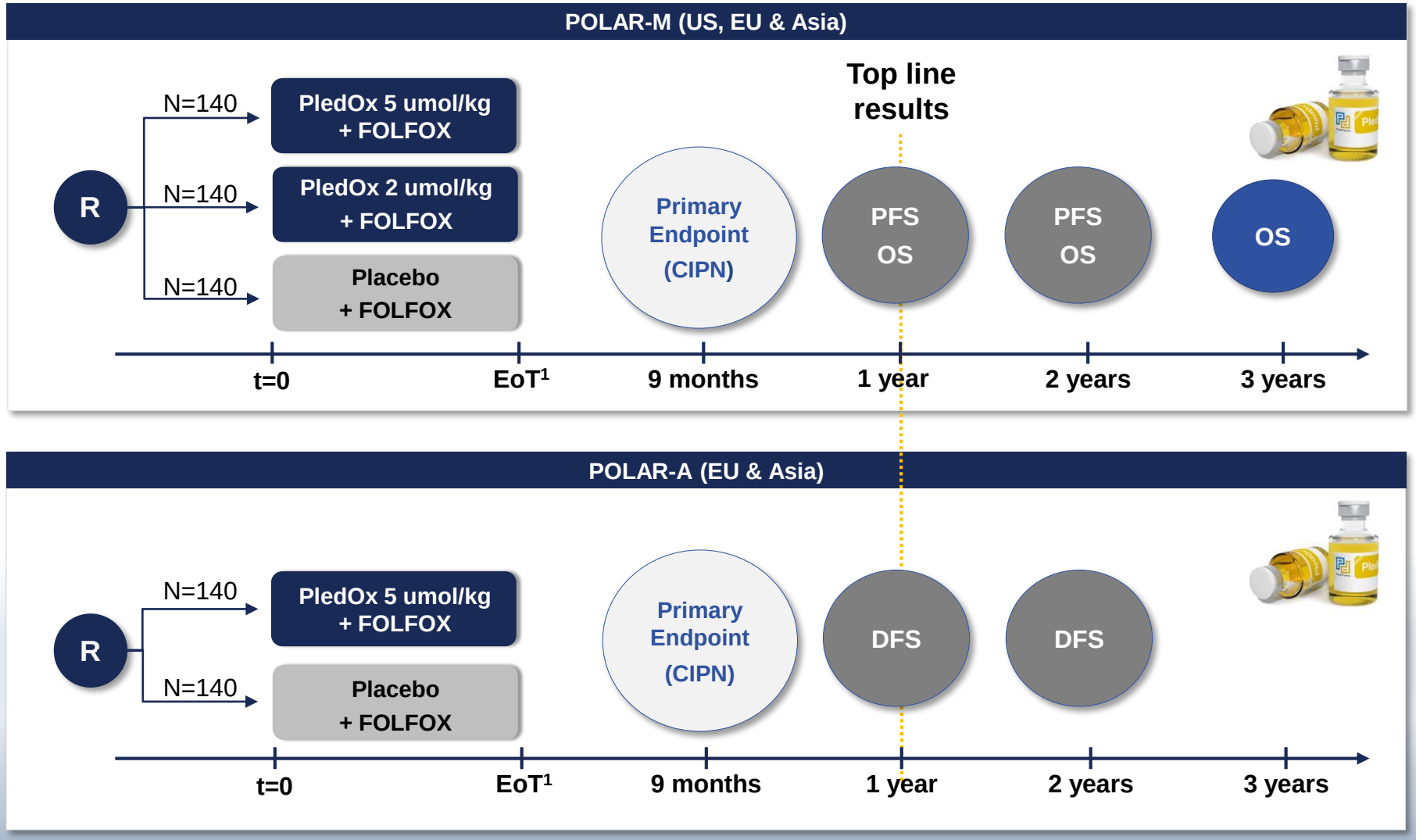
- Impact on progression free survival (PFS; POLAR-M), overall survival (OS; POLAR M) and disease free survival (DFS; POLAR A) assessed after 1 and 2 years (and 3 years for OS)

Timelines

- Patient recruitment to the global phase III studies in US, EU and Asia is ongoing.
- POLAR A expected to be fully recruited before yearend 2019 - top line results before year end 2020
- POLAR-M study expected to be fully recruited in Q2 2020 - top line results approximately a year later

Note: (**1**) FACT/GOG-Ntx is a validated, relevant & sensitive patient reported outcome instrument for scoring, analysis and interpretation of neuropathy in a disease specific target patient population used in ~6,700 patients in 34 studies.

Design of POLAR-studies



 Note: (**1**) End of treatment.

PledOx®– License agreements with Solasia in Nov 2017 and Sept 2019(1) for development and commercialization in Asia

1

- PledOx® for Chemotherapy Induced Peripheral Neuropathy (CIPN) – caused by any chemotherapy in any cancer type.
- License to develop and commercialize PledOx® in Japan, China, Hong Kong, Macau, South Korea, and Taiwan.

2

- Solasia will pay upfront, development, regulatory and sales milestones of up to 100 MUSD (~980 MSEK)[2]. To date, upfront and development milestones of ~7.5 MUSD have been received.
- Solasia will pay industry standard royalty rates on sales applicable for an in licensed asset in Phase III development.

3

- Solasia is **fully financing the expansion** of the Phase III program (POLAR-A and POLAR-M) to include Asian patients, supported by Japanese PMDA.
- PledPharma and Solasia will share all development costs beyond the initial indication, CIPN with oxaliplatin.
- The Phase I study in Japanese and Caucasian Healthy Volunteers with focus on safety, tolerability and pharmacokinetics showed positive results. Fully financed by Solasia.

Note: (**1**) Sept 2019 – Entered a comprehensive extension of the original license agreement (CIPN with oxaliplatin only) announced in November 2017. The extension covers the use of PledOx as prevention of CIPN by any chemotherapy in any cancer type, (2)Contract based on JPY, the amount given in USD and SEK is subject to exchange rates.

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Key value drivers of Asia licensing agreement

Solasia

Partnership with Solasia and its capabilities

3-4 years of accelerated development in Asia

Milestones & Royalties

Expansion of Phase 3 program will further enhance robustness

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PledOx® – development timeline

2018

- ✓ Results Ph.1 Study JPN
- ✓ Asian expansion of POLAR studies
- ✓ POLAR CTAs approved in US,JPN, UK, Spain, Italy, France & Belgium
- ✓ First Patient In (POLAR studies)

2019

- ✓ Further CTA approvals
- ✓ Initiate Indication expansion in taxanes
- All patients randomized POLAR A
- Scientific Advisory Board for Clinical development in CIPN with taxanes

2020

- All patients randomized POLAR M
- Results from pre clinical studies in taxanes
- POLAR A - Top line results of primary endpoint (CIPN) and key safety endpoints

2021

- POLAR M - Top line results of primary endpoint (CIPN) and key safety endpoints (1 year PFS&OS)
- Initiation of regulatory submissions

2022

First launch

2032

Calmangafodipir composition of matter patent expires

Epidemiology - Colorectal cancer (CRC) is the third most commonly diagnosed cancer

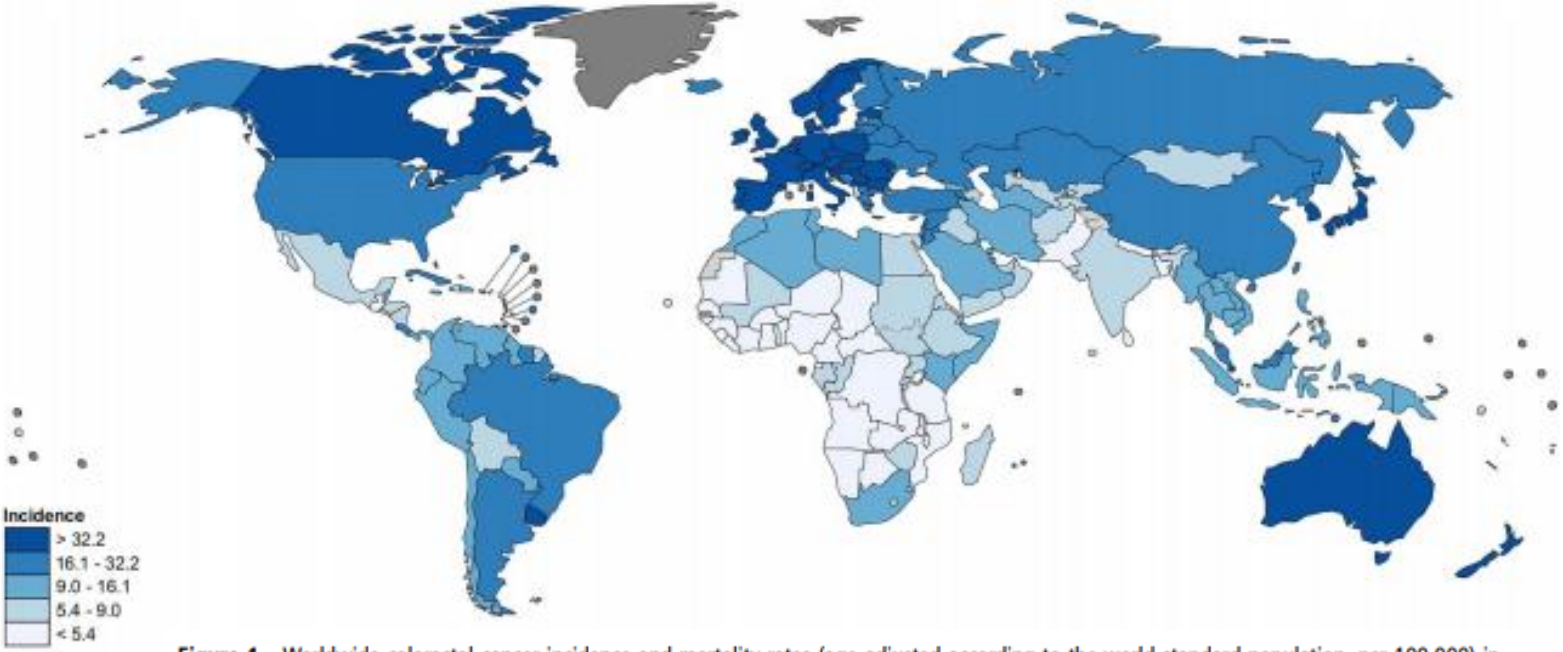


Figure 1 Worldwide colorectal cancer incidence and mortality rates (age adjusted according to the world standard population, per 100 000) in males in 2012 (GLOBOCAN 2012[1]).

"…and its burden is expected to increase by 60% by 2030"

 BMJ: Arnold M, et al. Gut 2016

Colorectal Cancer – Common treatment approaches

Stage I & II

- Surgery +/- RT
- Surgery + systemic therapy +/- RT (high-risk patients)

In early stages of disease, surgery has a high cure rate; many patients do not require additional systemic therapy

Stage III (adjuvant)

- Surgery + systemic therapy +/- RT

Common Systemic Therapies:

- FOLFOX
- CAPOX
- Capecitabine

Stage IV (metastatic)

- Systemic therapy +/- RT
- Surgery + systemic therapy +/- RT (resectable disease)

1L:

- FOLFOX + bevacizumab
- FOLFIRI + bevacizumab
- FOLFOX

2L (dictated by 1L therapy):

- FOLFIRI or FOLFOX + bevacizumab
- FOLFIRI
- FOLFIRI + cetuximab (KRAS+) or aflibercept
- KEYTRUDA (MSI-H or dMMR)

3L:

- Regorafenib
- Capecitabine
- Panitumumab (KRAS+)

While markets vary, FOLFOX +/- targeted therapy is the most commonly used first-line cytotoxic regimen for the systemic treatment of both Stage III and Stage IV CRC

- CAPOX, capecitabine + oxaliplatin
- FOLFOX, 5-FU + leucovorin + oxaliplatin
- FOLFIRI, 5-FU + leucovorin + irinotecan

Chemotherapy Induced Peripheral Neuropathy - Competitive landscape

COMMON TREATMENT APPROACHES FOR CIPN

Prevention

No approved drug for prevention or treatment of Chemotherapy Induced Peripheral Neuropathy

Treatment of Symptoms

Duloxetine (Cymbalta®)

Tricyclic Antidepressants

Gabapentin

Pregabalin (Lyrica®)

CIPN EMERGING TREATMENTS

MN-166
(Inflammation target)
Medicinova
Ph I study start announced in Mar-2018

APX-3330
(APE1/Ref1)
Apexian
Ph I SAD study start in Jan-2018

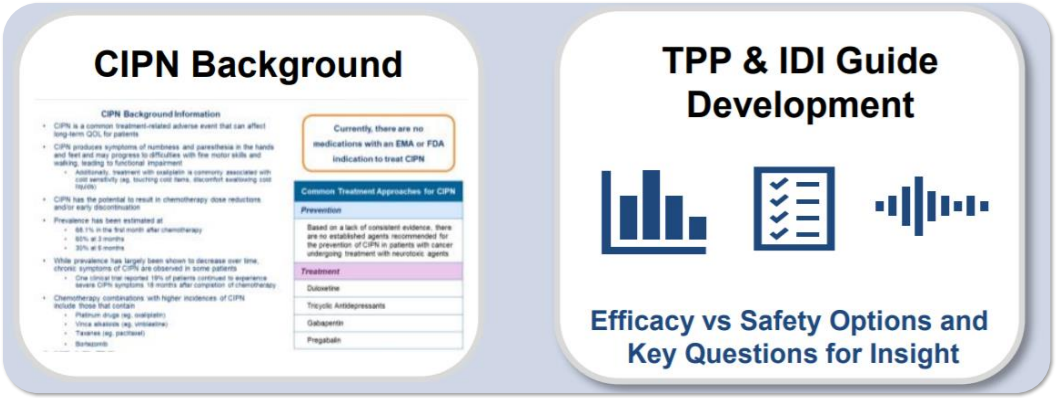
E-52862
(Sigma-1 Receptor)
Mundipharma
Ph II results published in Sept-2017

ART-123
(Thrombin [Coagulation Factor IIa])
Asahi Kasei Pharma
Japanese development

PledOx®
PledPharma

Phase I → **Phase II** → **Phase III**

PledOx® – Market Research, Pricing & Reimbursement



Physicians and Payers expressed high interest in PledOx® as a preventive treatment for CIPN.

Payer clinical evidence needs forms strategy for Phase III data collection

CIPN market research with US and EU Oncologists and Payers to gain insight and validation

- Confirms unmet needs in CIPN
- Verifies PledOx® Target Product Profile

Market Research Overview:
1:1, blinded, in-depth interviews
Physicians and Payers were recruited as follows:

🇺🇸	6 Physicians, 6 Payers
🇫🇷	2 Physicians, 2 Payers
🇩🇪	2 Physicians, 2 Payers
🇬🇧	2 Physicians, 2 Payers

 Note: (**1**) Oncologists from US and EU3. Payers from US (National MCO, Regional HMO, Medicare, Academic/Integrated System) and EU3.

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CIPN associated with high health care costs in the US

Research Article

Healthcare Costs and Workloss Burden of Patients with Chemotherapy-Associated Peripheral Neuropathy in Breast, Ovarian, Head and Neck, and Nonsmall Cell Lung Cancer

Crystal T. Pike,[1] Howard G. Birnbaum,[1] Catherine E. Muehlenbein,[2] Gerhardt M. Pohl,[2] and Ronald B. Natale[3]

- Privately insured administrative claims database study (Ingenix Employer db, 4.7 million people)
- Patients with qualifying tumors, and claims for chemotherapy and services indicative of CIPN
- Patients <65 years of age
- Cases were matched 1:1 to controls with no CIPN-related claims based on demographics, diabetes history and propensity for having a diagnosis of PN during the study period

Increased health care costs for CIPN patient:

17,344 USD

during first year after chemotherapy

On average, each CIPN case had 12 more outpatient visits than controls, and spent more days in the hospital

 Pike et al (2012) Healthcare Costs and Workloss Burden of Patients with Chemotherapy-Associated Peripheral Neuropathy in Breast, Ovarian, Head and Neck, and Nonsmall Cell Lung Cancer.

Payer Insight & combined EMA Scientific & Payer Advice

- clarifies data collection in Phase 3 to build robust pricing arguments

- With PledOx being first-in-class
  - Important to provide information of disease burden, unmet need, and costs of not treating or inadequately treating CIPN

'You're pushing an unopen door with CIPN in that Oncs are aware of its existence and how troublesome it can be, but nothing has been assessed in this space previously'

Pricing assumption based on base-case target product profile[1]

1,000 USD/cycle

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

NICE National Institute for Health and Care Excellence

Statens legemiddelverk

- Collection of data in POLAR studies extended to capture key variables associated with CIPN costs: hospital visits, medicines, medical procedures and events
- Draft cost-effectiveness model developed to be updated with POLAR efficacy study data and included in Payer dossier

Note: (**1**) interviews with Oncologists from US and EU3; price comparators branded Lyrica and Cymbalta.

PledOx® – Commercial potential in CRC patients

~700k

Drug treated CRC patients in US, EU5 & JPN/year

~225k

Number of oxaliplatin treated patients in US, EU5 & JPN/ /year

~1.5m

Number of oxaliplatin cycles in US, EU5 & JPN /year

Pricing assumption

1,000
USD/cycle

COGS assumption

Low single digit percent

+60%

in CRC incidence by 2030

10 years composition of matter patent protection assuming launch 2022 (without any patent extension)

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PledOx® Summary and Opportunities in CIPN with oxaliplatin

PREVENTS NERVE DAMAGE CAUSED BY OXALIPLATIN TREATMENT

DEVELOPMENT STATUS

- Phase II data provide reason to believe in Phase III
- Global Phase III POLAR studies approved in US, EU and Japan and first patient included – November 2018
- Asian expansion of Phase III supported by Japanese PMDA. First patient, in January 2019
- First Top-line results in POLAR-studies expected 2020 with regulatory submissions starting in 2021
- Indication expansion initiated - CIPN associated with taxanes

BUSINESS OPPORTUNITY

- CRC 3rd most diagnosed cancer
- ~1.5M cycles of oxaliplatin yearly (US, EU5, JPN)
- 60% growth in CRC incidence by 2030
- High incidence of CIPN (40-60%) in CRC patients.
- 20-30% of patients with symptoms >7 years later
- No available prevention or treatment of CIPN
- Limited competition
- Pricing and Reimbursement Research suggests a base-case pricing of 1,000 USD/cycle
- Life-cycle management initiatives to broaden the addressable market into CIPN associated with taxanes

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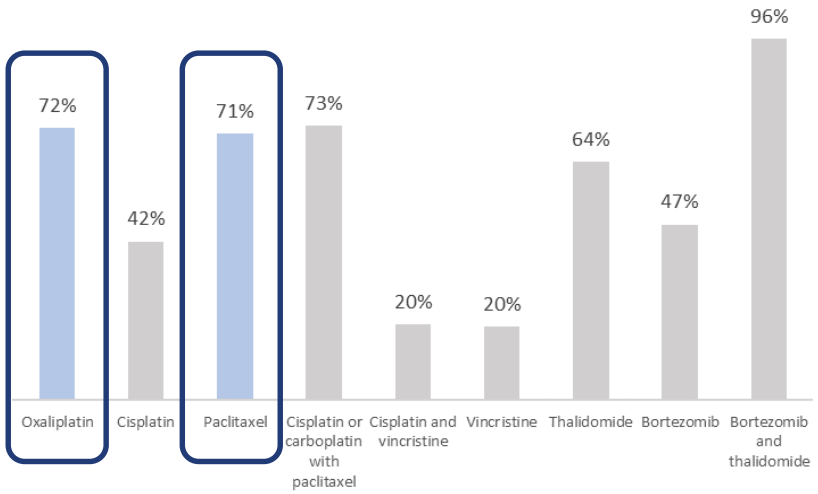
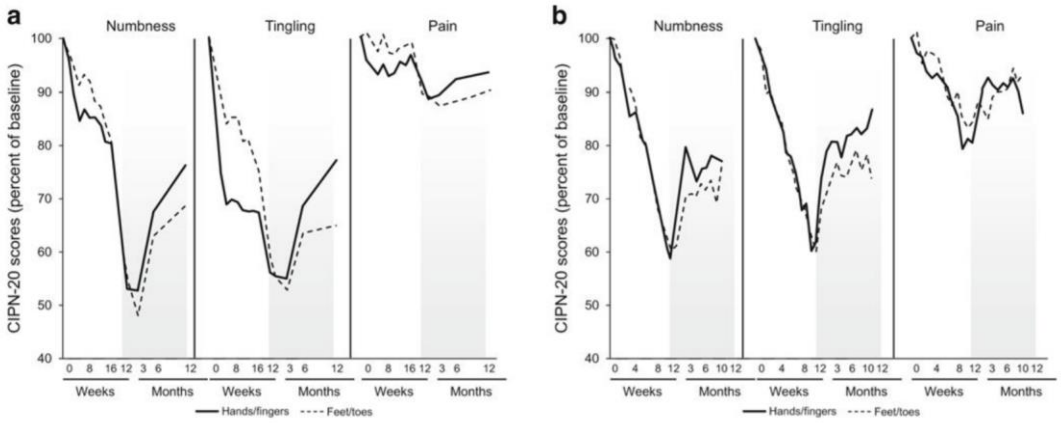
Expand into CIPN with taxanes - Unmet medical need is similar to that for oxaliplatin



- Similar percentage of patients experience CIPN with oxaliplatin and paclitaxel(1)
- Learnings from in CIPN/oxaliplatin can be leveraged to CIPN/taxanes
- Mechanism of Action (MoA) mitochondrial dysfunction a contributing factor to CIPN by taxanes

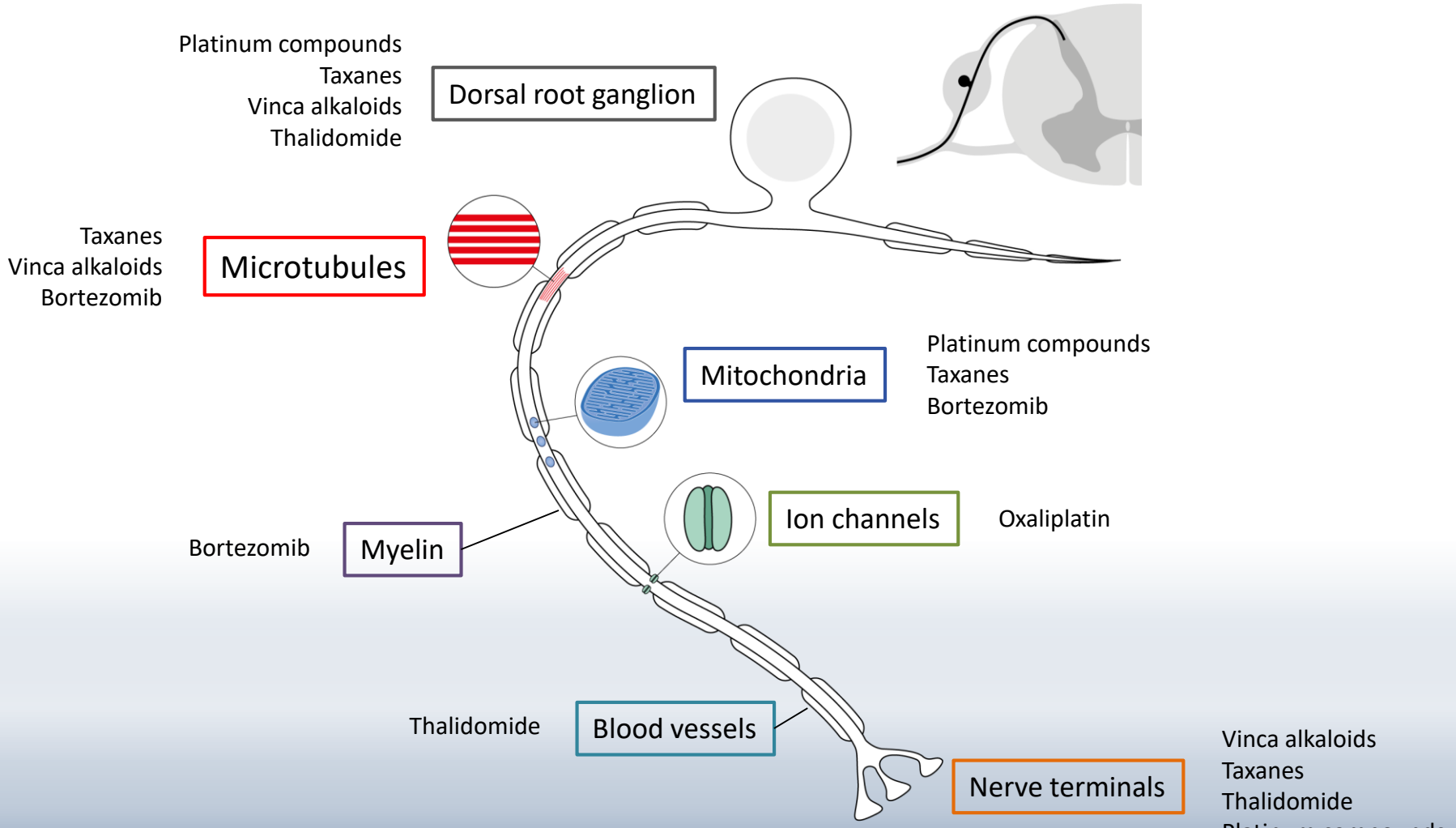
Oxaliplatin **Paclitaxel**



- Similar type of chronic CIPN symptoms are experienced, i.e. numbness, tingling in hands and feet(2)
- Coasting pronounced with oxaliplatin, not with paclitaxel(2)
- Acute symptoms with paclitaxel include aching pain, for oxaliplatin cold sensitivity(2)

(1) Seretny et.al (2014) Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis
(2) Pachman et.al (2017) Comparison of oxaliplatin and paclitaxel-induced neuropathy

Mitochondrial dysfunction a contributing factor to CIPN by taxanes give reasons to believe in PledOx®

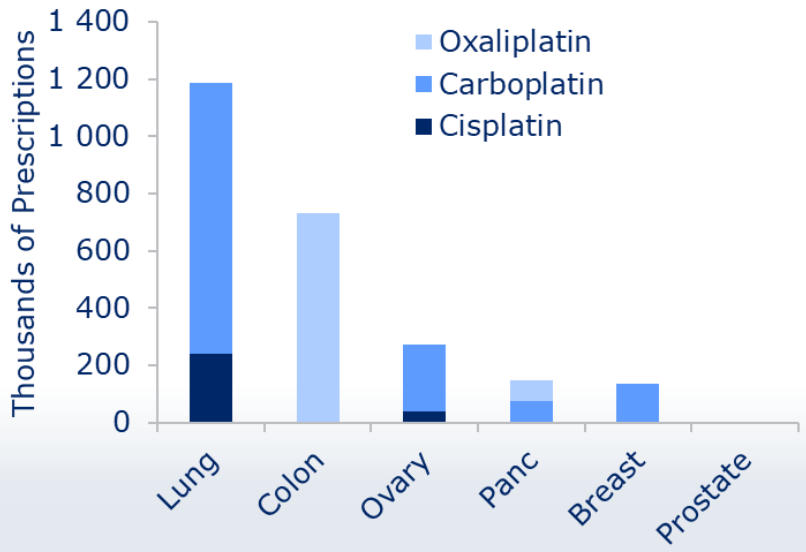


Kerckhove et.al (2017) Long-Term Effects, Pathophysiological Mechanisms, and Risk Factors of Chemotherapy-Induced Peripheral Neuropathies: A Comprehensive Literature Review
Park et al (2008) Mechanisms underlying chemotherapy-induced neurotoxicity and the potential for neuroprotective startegies

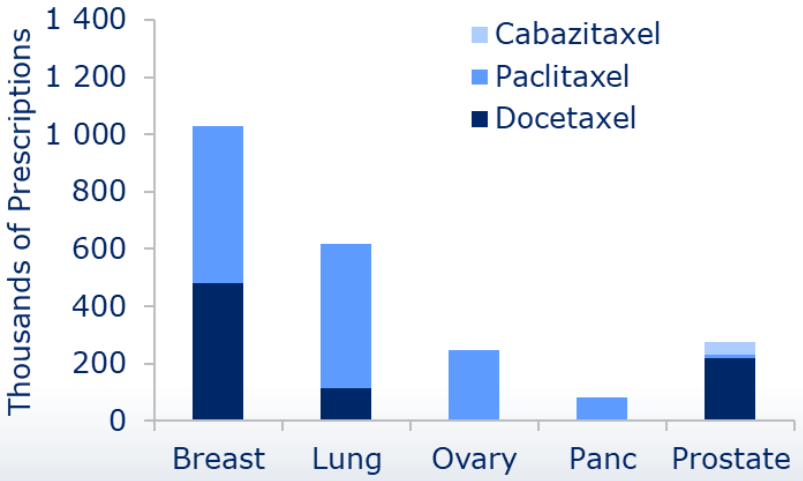
Attractive commercial opportunity in CIPN/taxanes

Market size: Taxanes have a significant use in clinical practice across several different cancer types (e.g. breast and ovarian cancer) with approximately 400,000 patients treated yearly in the US, EU5 and Japan

Use of platinum-based chemotherapy by tumor type



Use of taxane-based chemotherapy by tumor type



Competitive landscape

No competitor clinical trials registred on clinicaltrials.gov

IMS Health (2015); US data

Next steps in development path for CIPN/taxanes

Pre-clinical studies and Scientific Advisory Board for Clinical development (2019/2020)

Pre-clinical studies in collaboration with Prof Cavaletti, Univ Milano-Biocca

1) Preliminary dose-ranging study with PledOx®

2) Efficacy of PledOx® will be evaluated vs placebo on top of paclitaxel (taxane) alone or in combination with carboplatin

Regulatory interactions (2019-2020)

Clarify development path, including

a) Requirements for clinical efficacy & safety data for sNDA/MAA – how to leverage POLAR study data?
b) Design of clinical study incl endpoints, sample size etc
c) Dose selection in CIPN/taxanes

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PledPharma

Paracetamol (acetaminophen) poisoning … no adequate treatment for high risk patients

19bn units of paracetamol packages sold every year in the US.

Minimum toxic dose of paracetamol in adults – only 7.5g

~50 % of overdoses are unintentional

Could lead to acute liver failure, liver transplant or death

89,000 cases of paracetamol overdose in US per year

105,000 cases of paracetamol overdose in UK per year

No adequate treatment for high risk patients

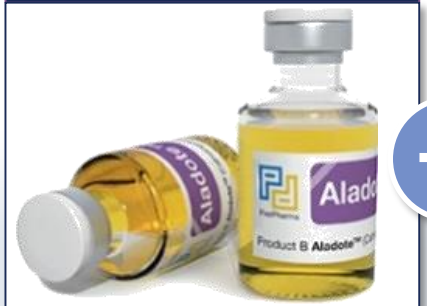
Aladote® – protects the liver and reduce the risk of acute liver failure

Aladote®

aims to become new standard of care for high risk patients

Prevents acute liver injury caused by paracetamol (acetaminophen) poisoning…

Aladote®

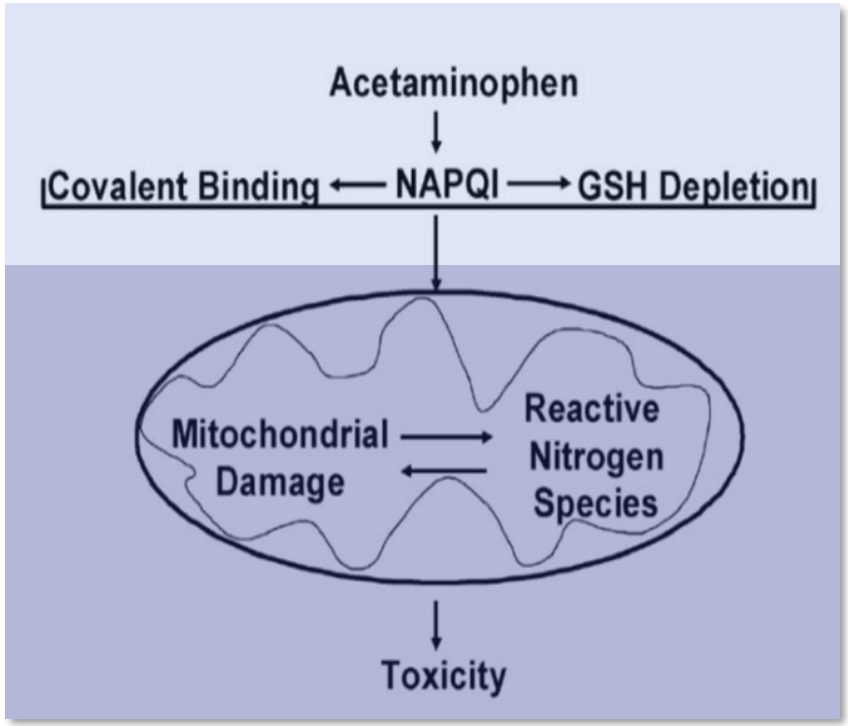


Acetylcysteine (NAC)

… in high risk patients where treatment of NAC is not adequate:

~ 25% of patients are late arrivals to hospitals (>8h)
~ 13% arrive early with high level of paracetamol

Aladote has potential for reducing APAP-induced acute liver injury in high risk patients

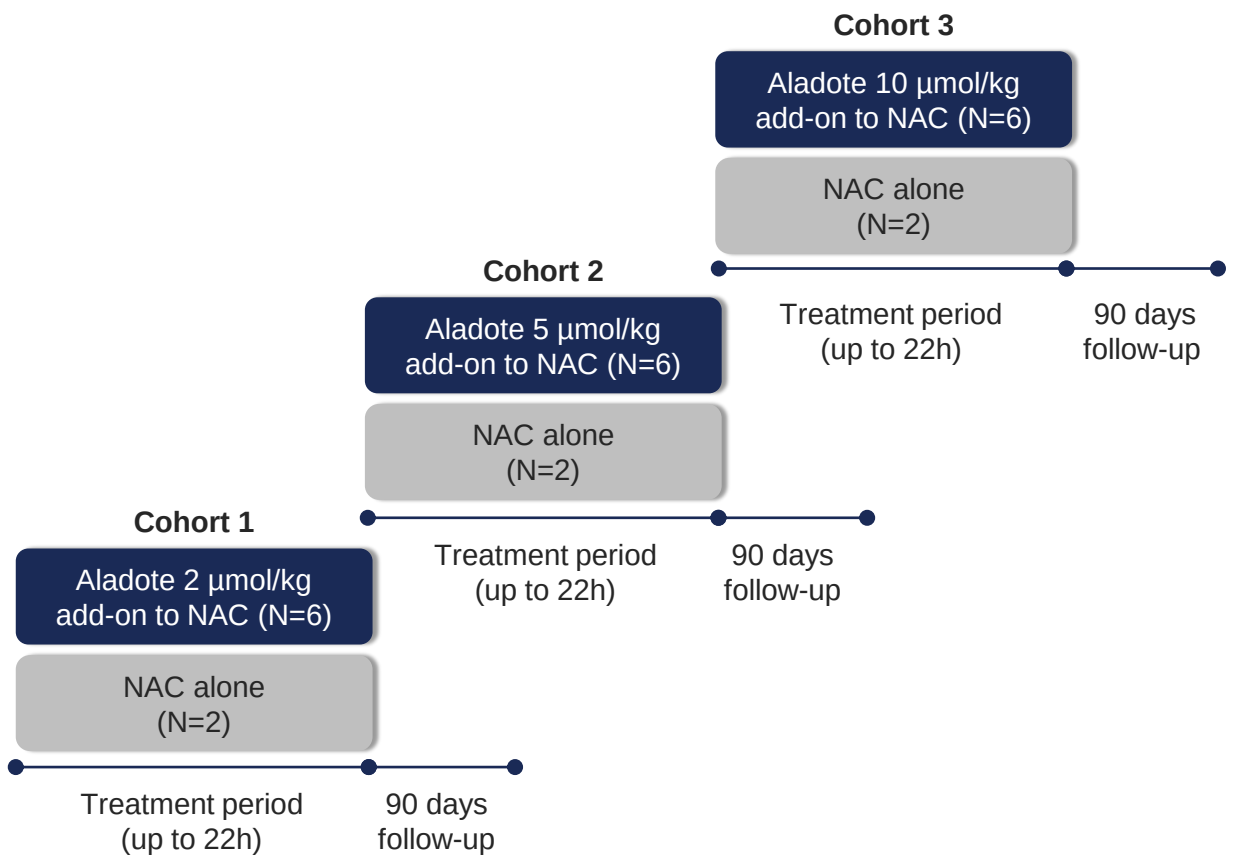


Source: Burke et al. 2010

- APAP overdose leads to formation of the toxic metabolite NAPQI
- In the metabolic phase, this leads to depletion of reduced glutathione (GSH) and binding of NAPQI to liver proteins
  - NAC is effective in this phase by replenishing GSH
  - However, the effectiveness depends on the amount of APAP overdose and timing of NAC
- In parallel, the oxidative phase occurs in the mitochondria, leading to subsequent cell death when GSH is significantly depleted
  - NAC is ineffective in this phase once GSH is significantly depleted
  - Aladote can inhibit oxidative pathways and thereby potentially preventing Acute Liver Injury

Design of Aladote Phase Ib/IIa clinical study

Randomised Open Label Exploratory, Safety and Tolerability Study with Calmangafodipir in Patients Treated with the 12-hour Regimen of N-Acetylcysteine (NAC) for Paracetamol Overdose



Design

- Single ascending dose study in 3 dosing cohorts of 8 patients (N=24) as add-on to NAC regime

Patients

- Admitted to hospital within 24h of paracetamol overdose requiering NAC treatment

Treatment

- Aladote/Placebo administered 2 hrs after NAC loading dose

Endpoints

- Safety and tolerability
- Biomarkers[1] of liver status

 Note: (**1**) Conventional biomarker ALT and experimental biomarkers such as microRNA-122 (miR-122) and Keratin-18 (K18)

Aladote® positive pre-clinical and clinical data provides reasons to believe … motivates further development

Phase Ib/IIa Study – Positive results

- Randomized Phase Ib/IIa in paracetamol overdosed patients
- In total 24 patients, were recruited to three Aladote® doses as add-on to NAC regime versus NAC alone
- Met the primary endpoint of safety and tolerability in the combination of Aladote® and NAC
- Results indicate that Aladote® may reduce liver injury based on measurement of the pre-defined exploratory biomarkers, Keratin-18 (K18) and microRNA-122 (miR-122) in patients treated with Aladote® and NAC compared to NAC alone[1]

Clinical Study results presented at the 58th Annual Meeting of the Society of Toxicology in March, in Baltimore, at EASL ILC in April, Vienna and published in Lancet's journal EBioMedicine in July 2019

 Note: (**1**) See p.71 for details on biomarkers such as Alanine transaminase (ALT) , Keratin-18 (K18) and microRNA-122 (miR-122).

Met the primary endpoint of safety and tolerability in the combination of Aladote® and NAC

Event	NAC alone	NAC + 2 µmol/kg Aladote	NAC + 5 µmol/kg Aladote	NAC + 10 µmol/kg Aladote
Any adverse event	6 (100%)	6 (100%)	6 (100%)	6 (100%)
Any serious adverse event	2 (33%)	4 (67%)	2 (33%)	3 (50%)
Serious adverse event starting within 7 days	1 (17%)	1 (17%)	1 (17%)	2 (33%)

No AE or SAE probably or definitely related to Aladote

Liver injury – (pre-defined secondary outcome)

Event	NAC alone	NAC + 2 µmol/kg Aladote	NAC + 5 µmol/kg Aladote	NAC + 10 µmol/kg Aladote
50% ALT increase	2 (33%)	0 (0%)	0 (0%)	1 (17%)
100% ALT increase	1 (17%)	0 (0%)	0 (0%)	1 (17%)
ALT >100 U/L at 10 hours	2 (33%)	0 (0%)	0 (0%)	0 (0%)
ALT >100 U/L at 20 hours	2 (33%)	0 (0%)	0 (0%)	0 (0%)

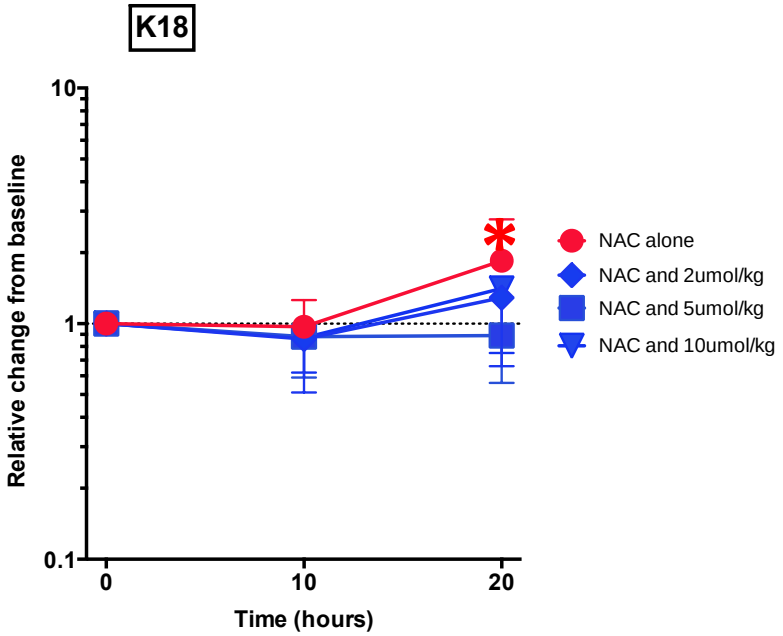
ALT >100 U/L is the indication to stay in hospital

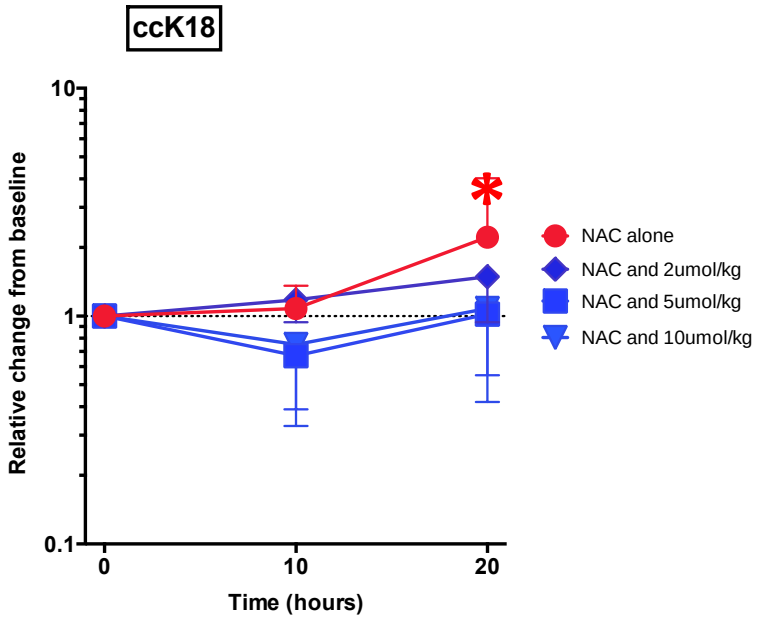
Patients in need of additional NAC infusions after the planned 12 hrs NAC infusion, n (%):

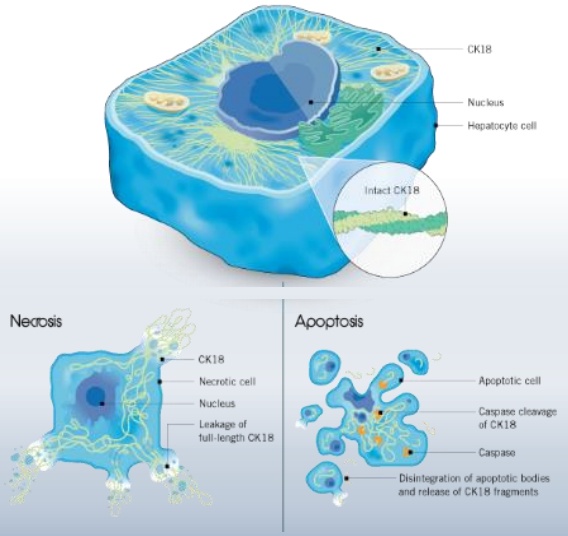
- **NAC alone: 3 (50%)**
- **NAC+Aladote: 2 (11%)**

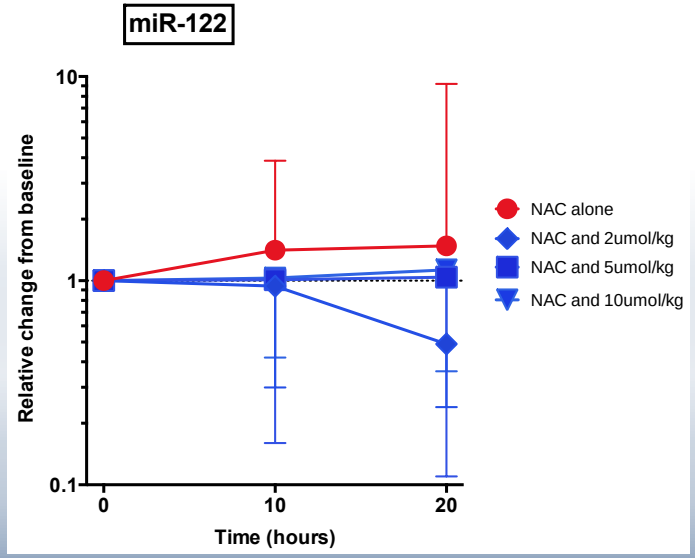
NAC+2µmol/kg: 1 (17%); NAC+5µmol/kg: 0 (0%); NAC+10µmol/kg: 1 (17%)

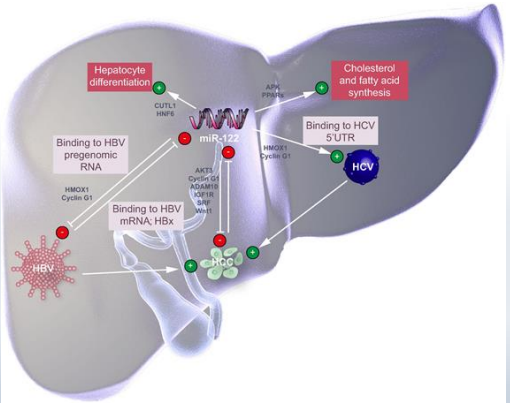
Liver injury – (pre-defined secondary outcome)



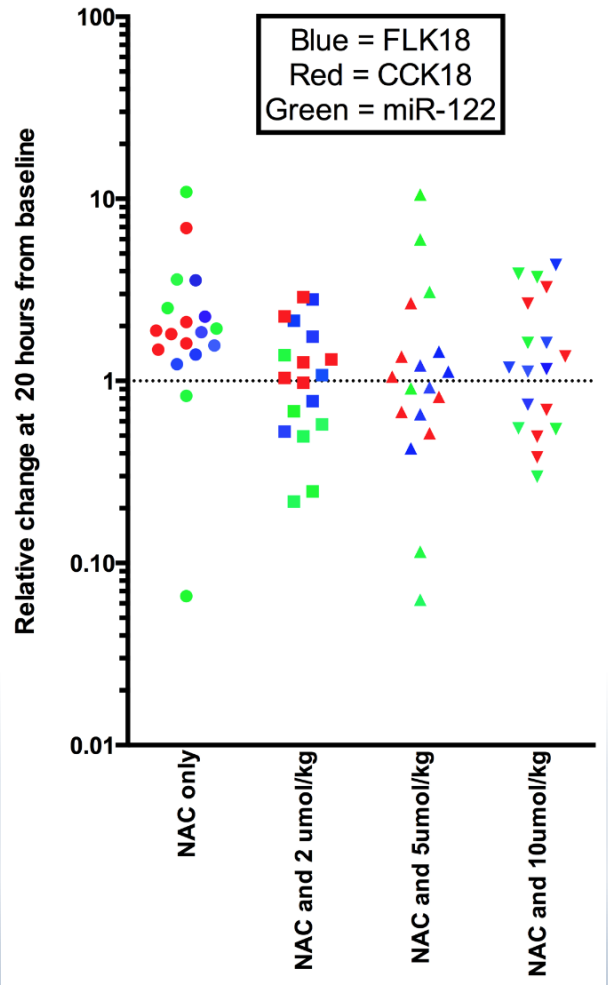








Liver injury – (pre-defined secondary outcome)



All patients with NAC alone had an increase in both K18 isoforms (FLK18 and CCK18)

- K18 (Patients with decreased levels from baseline to 20hrs: n (%)):
  - NAC alone: 0 (0%); NAC+Aladote: 6 (33%)
    - NAC+2µmol/kg: 2 (33%); NAC+5µmol/kg: 3 (50%); NAC+10µmol/kg: 1 (17%)
- CCK18 (Patients with decreased levels from baseline to 20hrs: n (%)):
  - NAC alone: 0 (0%); NAC+Aladote: 7 (39%)
    - NAC+2µmol/kg: 1 (17%); NAC+5µmol/kg: 3 (50%); NAC+10µmol/kg: 3 (50%)
- miR-122 (Patients with decreased levels from baseline to 20hrs: n (%)):
  - NAC alone: 2 (33%); NAC+Aladote: 11 (61%)
    - NAC+2µmol/kg: 5 (83%); NAC+5µmol/kg: 3 (50%); NAC+10µmol/kg: 3 (50%)

Aladote® granted Orphan Drug Designation by the FDA (March 18, 2019)

PledPharma

PRESSRELEASE

PledPharma's drug candidate Aladote® granted Orphan Drug Designation

Stockholm, March 18, 2019. PledPharma AB (publ) today announces that the U.S. Food and Drug Administration (FDA) has granted an Orphan Drug Designation (ODD) to the drug candidate Aladote®, in development for reducing liver damage due to paracetamol overdose.

Today's treatment for overdose of paracetamol, N-acetylcysteine (NAC), is most effective if given within eight hours of the overdose. Patients arriving later to the hospital, and for those with a severe overdose, there is a need for more efficacious treatment options. Aladote® is a first-in-class drug candidate in development to reduce liver damage due to paracetamol overdose.

The scientific rationale as well as clinical results from the completed proof-of-principle study indicate that Aladote® in combination with NAC has the potential to reduce liver damage in the specified patient population. PledPharma intends to conduct regulatory interactions to determine the next step in development of Aladote®.

ODD benefits

- Lowered development cost – driven by patient safety and efficacy requirements (typically < 300 patients in Phase II / III studies)
- Shortened development time
- Commitment of the regulators to support development
- Early exposure of a drug to regulators
- 7-year Marketing Exclusivity if first approved
- Tax credits (-50%) for qualified clinical trial cost
- Waiver of NDA user fees (– over US$2 million)

Tentative study design for next clinical study - pending finalization after regulatory interactions[1]

Design item	
Patient population	High risk POD patients (Early >300 nomogram OR Late (>8h) with >20mg/L paracetamol) requiring treatment with NAC
NAC regims	12 hr or 21 hr regims
Initiation of randomized treatments	IV (bolus) as soon as possible after randomization and after starting NAC (but no later than 4 hours after starting NAC)
Treatment arms	3 arms Aladote high-dose; Aladote low-dose; Placebo
Sample size	TBD
Key efficay endpoints	% change from baseline to end of first NAC regime in K18 Number (%) of patients that need further NAC after 12h/21h ALT >100 IU/L or doubled at end of treatment Experimental biomarkers for liver injury (miR-122 and GLDH) Length of hospital stay
Study countries	EU, US (4-8 sites)

 Note: (**1**) regulatory interactions planned for Q4 2019

Aladote® – timeline

2018

- ✓ Ph Ib/IIa study fully recruited
- ✓ Initial Results Ph Ib/IIa study
- ✓ Established Scientific Advisory Board
- ✓ Full results Ph Ib/IIa study
- ✓ Submission of Orphan Drug Designation

2019

- ✓ Orphan Drug Designation granted in the US
- ✓ Presentation of study results at Society of Toxicology
- ✓ Presentation of study results EASL ILC
- ✓ Presentation of results in Lancet EBiomedicine
- Regulatory interactions – development program

2020

- Initiate next study - subject to regulatory interactions

2023

- Regulatory submissions start

2032

Calmangafodipir composition of matter patent expires

POD incidence in EU5 and US – Hospital visits 2018

 Note: Paracetamol (acetaminophen) Overdose 2018 estimate Epidemiology.

Burden on society - POD US Healthcare Costs were $1bn in 2010

In the US the annual cost in 2010 was estimated at $1,059 million to treat Patients with POD

The POD Emergency Department and inpatient cost is around $13K-40K

The average POD inpatient length of stay was 3.1 Days, with a variance of + 4.4 Days for the most severe cases

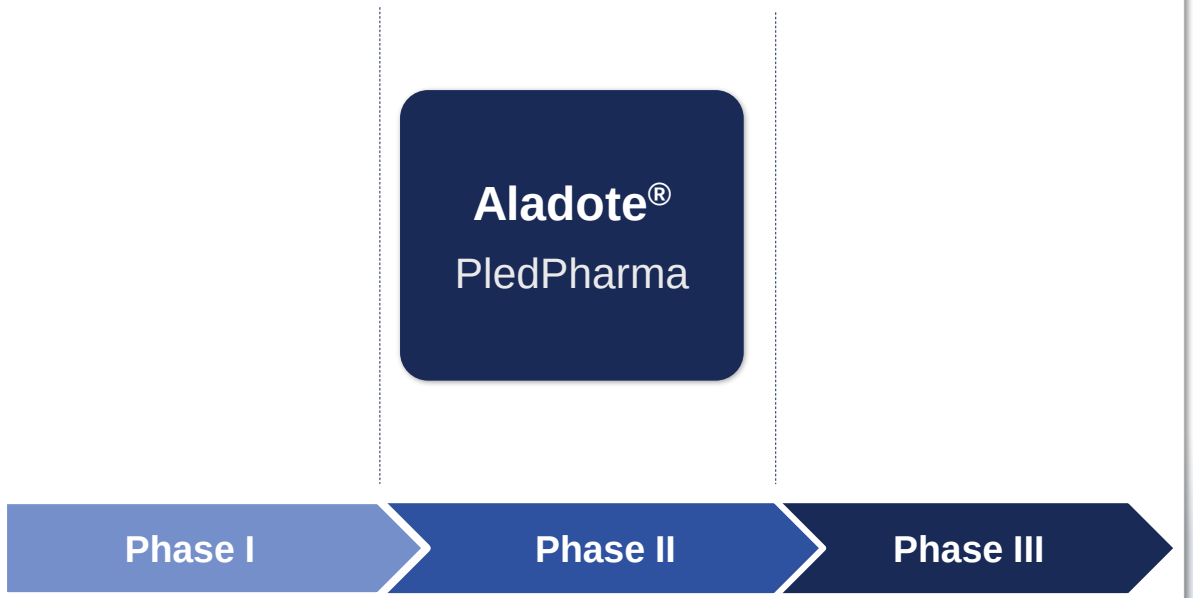
US liver transplant costs $125-473K

Note: Adapted from: Altyar A. Clinical and economic characteristics of emergency department visits due to acetaminophen toxicity in the USA BMJ Open 2015;5

No competitor in development

TREATMENT APPROACHES FOR POD
Active Charcoal
N-Acetylcysteine (NAC)
Liver transplant

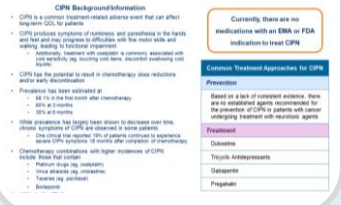
POD EMERGING TREATMENTS



Aladote® – Initial Market Research, Pricing & Reimbursement

Market research with US and EU Physicians and Payers to gain insight into unmet needs, validate Target Product Profile and Pricing & Reimbursement

POD Background



TPP & IDI Guide Development

Efficacy vs Safety Options and Key Questions for Insight

Testing

12 Physicians and 12 Payers

Team Expertise

24 qualitative interviews comprised

- 6 US payers, 6 EU3 (2 from each of D, F, UK)
- 6 US physicians, 6 EU3 (2 from each of D, F, UK)

Physician & Payer Insight

- Confirms the unmet medical need and verifies TPP
- Time in hospital a major driver of value in a cost-benefit analysis

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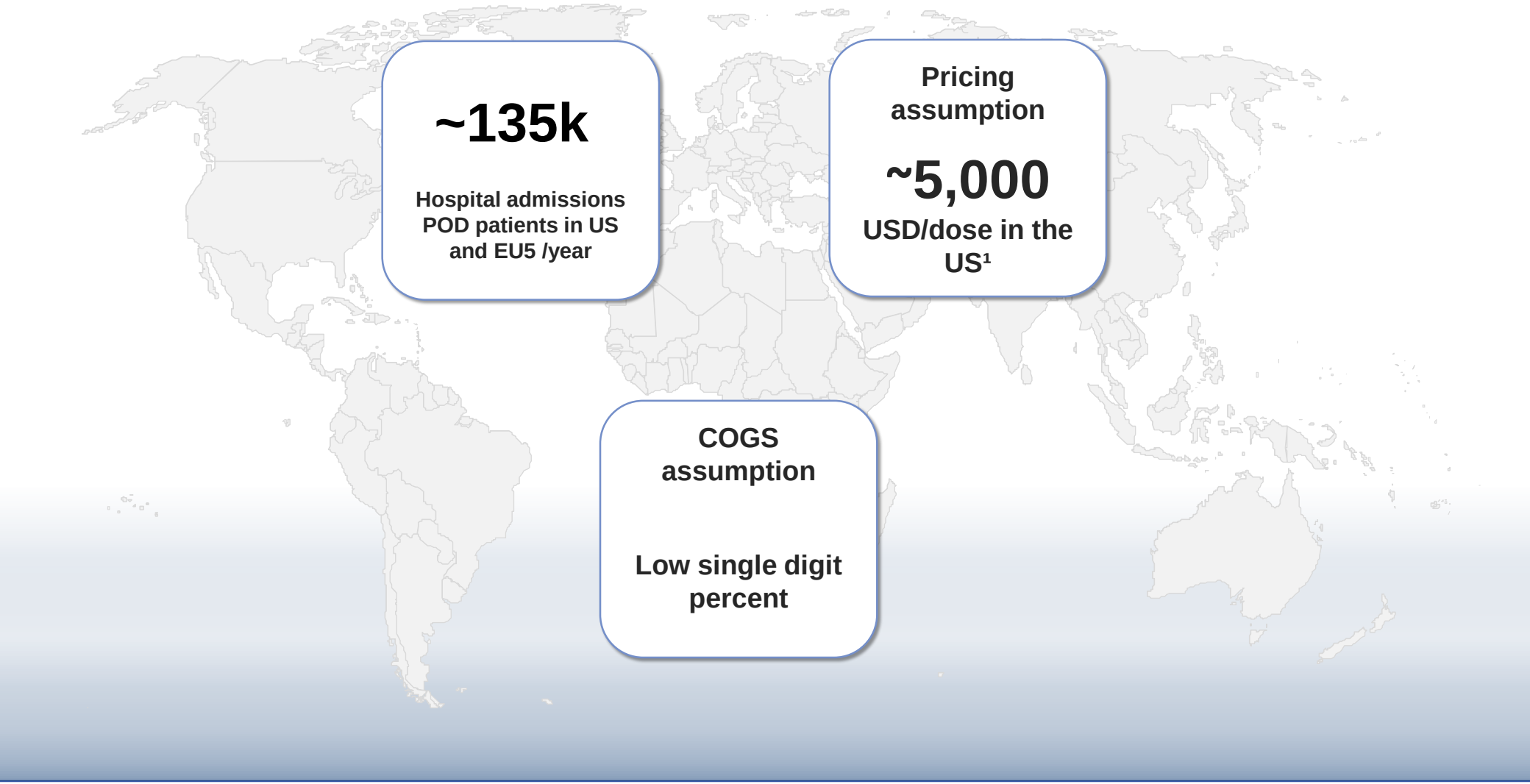
Aladote® – Commercial potential in POD patients



~135k

Hospital admissions POD patients in US and EU5 /year

Pricing assumption

~5,000

USD/dose in the US[1]

COGS assumption

Low single digit percent

 Note: **(1)** Up to $5000 based on initial and limited research

PiedPharma

Aladote® - Summary and Opportunities

PREVENTS ACUTE LIVER FAILURE CAUSED BY PARACETAMOL (ACETAMINOPHEN) POISONING

DEVELOPMENT STATUS

- Positive study results Ph Ib/IIa announced in September 2018
  - Presented at the 58th Annual Meeting of the Society of Toxicology in March, 2019
  - Presented at EASL ILC April, 2019
  - Published published in Lancet's journal EBioMedicine in July, 2019
- Orphan Drug designation granted March 2019 in the US
- Design of next study finalised together with Scientific Advisory Board - subject to regulatory interactions in Q4 2019

BUSINESS OPPORTUNITY

- Paracetamol (acetaminophen) poisoning is one of the most common sorts of overdoses
- No adequate treatment for high risk patients
- ~135K Hospital admissions POD patients in US and EU5 /year
- Price assumption, ~5,000 USD/dose[1] in the US based on initial market research

 Note: **(1)** Up to USD 5,000 based on initial and limited research

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PledPharma

Summary - Direction, opportunities and enablers to enhance value

1 PledOx®

- Huge unmet medical need with no treatment approved today
- Ongoing global phase III program in CIPN with oxaliplatin
- Expansion into CIPN with taxanes

2 Aladote®

- Substantial unmet medical for patients where NAC is not adequate
- Exciting results from first clinical study motivates further development
- Granted ODD by US FDA

3 Business development

- Strategic partnerships
- Maximise PledOx value
- Enhance value to the development of Aladote in an orphan setting

4 Financial

- Listing of shares on Nasdaq main market
- Cash position sufficient to top-line for the POLAR-studies, Pre-clinical taxanes/CIPN and Aladote next study*

5 People & Organisational

- Transformed organisation
- Proven track record in bringing products to the market

 Note: *Pending regulatory interactions

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PledPharma

Key management members

Nicklas Westerholm
CEO
- Before joining the PledPharma team in 2017, Nicklas worked in the AstraZeneca Group in various roles and business areas, most recently as VP in project & Portfolio Management.
- Ownership: 500,000 warrants

Yilmaz Mahshid
CFO
- Yilmaz has a Ph.D. from the Department of Medical Biochemistry and Biophysics at Karolinska Institute and has experience from the finance field as he has been at Industrifonden and Pareto Securities.
- Ownership: 250,000 warrants

Stefan Carlsson
CMO
- Stefan has a medical degree as well as a doctorate in physiology from Gothenburg University. He has a long experience from leading positions in preclinical and clinical drug development.
- Ownership: 250,000 warrants

Marie Bengtson
Client Project Director
- Marie has over 20 years of experience in clinical research and development in the pharmaceutical industry. She has worked at various international CRO and pharmaceutical companies, managing projects and clinical studies.

Anders Sveno
Head of CMC & Supply Chain
- Anders joined PledPharma from Meda/Mylan AB where he was in charge of regulatory CMC. He is an organic chemist with over 10 years of experience with active substance development at Astra Zeneca.

Helene Depui Ekdal
Clinical Development Director
- Before joining PledPharma, Helene worked as Senior Director, Global Value Chain leader at AstraZeneca. She has extensive experience of drug development from 25 years at Astra Zeneca, where she was involved in the development of e.g. BRILINTA®.

Christian Sonesson
VP Product Strategy & Development
- Christian was appointed VP in 2017 following a long and career at Astra Zeneca where he had mostly global development roles. Also, he holds an Executive MBA from Stockholm School of Economics and a doctorate in in biostatistics from Gothenburg University.
- Ownership: 200,000 warrants

Jacques Näsström
CSO
- Jacques was PledPharma's CEO prior to Westerholm. He is a pharmacist with a Ph.D. in Pharmacology from Uppsala University and an MBA from Stockholm School of Economics.
- Ownership: 80,452 shares and 20,000 warrants

Malin Nittve
Project Director & Regulatory Affairs
- Malin is a pharmacist with an MBA who has over 25 years of versatile experience, ranging from start-ups to major international pharmaceutical companies. She has past experience from product development, project management and regulatory affairs at various workplaces.

Mikael Carlsson
Controller

Scientific advisory board

Established for PledOx®

Professor Guido Cavaletti

- MD, Ph.D. and Head of the Neuroimmunology Center at S. Gerardo Hospital and the Experimental Neurology Unit at the School of Medicine, University of Milan-Biocca in Monza, Italy and international expert in chemotherapy induced peripheral neuropathy.

Professor Emeritus Bengt Glimelius

- MD, Ph.D. Professor emeritus in oncology at the University of Uppsala and Consultant at the University hospital. Coordinating principal investigator in the PLIANT trial - PledPharma's Phase IIb Study with PledOx®.

Associate Professor Rolf Karlsten

- MD, Ph.D. Specialist in anesthesiology, intensive care and neuropathic pain management. Head of Rehabilitation Medicine and Pain Center at Uppsala Academic Hospital.

Professor David Cella

- Ph.D., Chair of the Department of Medical Social Sciences at Northwestern University Feinberg School of Medicine in Chicago, USA. Expert in evaluations of patient-reported outcomes in clinical trials.

Fifth undisclosed member

- US expert and KOL In CIPN

Established for Aladote®

Dr. Richard C. Dart

- Ph.D., Chair of the Department of Medical Social Sciences at Northwestern University Feinberg School of Medicine in Chicago, USA. Expert in evaluations of patient-reported outcomes in clinical trials.

Professor Laura James

- MD, Associate Vice Chancellor for Clinical and Translational Research and Professor of Pediatrics at the University of Arkansas for Medical Sciences (UAMS) and Arkansas Children's Hospital System, USA.

Peter De Paepe

- MD, Professor in clinical pharmacology at the Heymans Institute of Pharmacology at Ghent University, and is currently head of the emergency department of the Ghent University Hospital in Belgium.

Board of directors

Håkan Åström

Chairman of the board

- Board member since: 2011
- Other assignments: Chairman of the boards of directors of Affibody Holding AB, Tubulus RP Förvaltning AB and MedCore AB. Board member of Ferrosan Medical Devices A/S and Rhenman & Partner Asset Management
- Ownership: 505,337 shares and 192,000 warrants

Marie Ekström Trägårdh

Board member

- Board member since: 2017
- Other assignments: CEO Sectra Imaging IT Solutions and Executive Vice President of the Group Sectra AB
- Ownership: 96,000 warrants

Sten Nilsson

Board member

- Board member since: 2013
- Professor in oncology with affiliation to the Karolinska Institute (KI), MD, Ph.D.
- Other assignments: Board member of the Swedish Cancer Society Research Council and Rhenman & Partner Asset Management
- Ownership: 1,100 shares and 35,000 warrants

Gunilla Osswald

Board member

- Board member since: 2017
- Ph.D. in biopharmacy and pharmacokinetics
- Other assignments: CEO BioArctic AB
- Ownership: 50,000 warrants

Elisabeth Svanberg

Board member

- Board member since: 2017
- MD, Ph.D., Assoc Professor in surgery
- Other assignments: Chief Development Officer Ixaltis SA. Board member Swedish Orphan Biovitrum (SOBI)
- Ownership: 96,000 warrants

Income statement

KSEK	2019 Jul-Sep	2018 Jul-Sep	2019 Jan-Sep	2018 Jan-Sep	2018 Jan-Dec
Revenue					
Sales	6,171	6,715	65,509	17,113	28,211
Other operating income	11	-	11	2	2
	6,182	**6,715**	**65,520**	**17,114**	**28,212**
Operating expenses					
Project costs	-33,633	-17,991	-85,974	-59,607	-83,855
Other external costs	-3,218	-2,460	-10,175	-8,734	-11,325
Employee costs	-4,569	-4,355	-15,818	-13,846	-20,034
Depreciation and impairment	-54	-	-156	-	-
Other operating revenues/expenses	-	-2,510	-2,755	-4,404	-5,511
Operating results	**-35,292**	**-20,601**	**-49,357**	**-69,477**	**-92,514**
Financial items					
Interest income and similar items	3,400	1,757	10,947	6,611	7,511
Interest expense and similar items	-1	-	-6	0	-1
Results after financial net	**-31,893**	**-18,844**	**-38,416**	**-62,866**	**-85,003**
Tax	-	-	-	-	-
Results after tax	**-31,893**	**-18,844**	**-38,416**	**-62,866**	**-85,003**
Statement of comprehensive income					
Other comprehensive income	-	-	-	-	-
Comprehensive income for the period	**-31,893**	**-18,844**	**-38,416**	**-62,866**	**-85,003**
Net earnings and comprehensive income is entirely attributable to parent company					
Share Data					
Number of shares at the end of period	53,533,321	48,666,656	53,533,321	48,666,656	48,666,656
Average number of shares during period	53,533,321	48,666,656	50,974,743	48,666,656	48,666,656
Result per share before dilution (SEK)	-0.6	-0.4	-0.8	-1.3	-1.7
Result per share after dilution (SEK)	-0.6	-0.4	-0.8	-1.3	-1.7
Equity per share (SEK)	5.0	5.0	5.0	5.0	4.5
Equity per share after dilution (SEK)	5.0	5.0	5.0	5.0	4.5

Note: (**1**) Q3 2019 report

Balance sheet and cash flow statement

KSEK	9/30/2019	9/30/2018	12/31/2018
ASSETS			
Non-current assets			
Tangible non-current assets	176	-	-
Total non-current assets	**176**	**-**	**-**
Current assets			
Accounts receivables	1,853	374	9,444
Other receivables	601	733	624
Prepaid expenses and accrued income	1,899	2,866	2,093
	4,352	3,974	12,161
Cash and bank balance	286,748	250,267	229,876
Total current assets	**291,100**	**254,241**	**242,037**
Total assets	**291,276**	**254,241**	**242,037**

KSEK	9/30/2019	9/30/2018	12/31/2018
Equity			
Share capital	2,818	2,561	2,561
Other capital contributions	705,278	618,598	618,598
Accumulated loss including net loss	-440,213	-379,661	-401,798
Total equity	**267,882**	**241,499**	**219,362**
Long-term liabilities	**117**	**-**	**-**
Current liabilities			
Accounts payable	2,909	6,814	15,174
Other liabilities	1,481	1,089	1,205
Accrued expenses and deferred income	18,887	4,840	6,296
Total current liabilities	**23,277**	**12,742**	**22,675**
Total equity and liabilities	**291,276**	**254,241**	**242,037**

KSEK	2019 Jul-Sep	2018 Jul-Sep	2019 Jan-Sep	2018 Jan-Sep	2018 Jan-Dec
OPERATING ACTIVITIES					
Result after financial net	-31,893	-18,844	-38,416	-62,866	-85,003
Adjustments for non-cash items*	-3,049	705	-3,865	-1,161	-1,700
Cash flow from operating activities before changes in working capital	**-34,942**	**-18,139**	**-42,281**	**-64,027**	**-86,703**
Changes in short term receivables	239	10,095	10,546	1,864	-6,273
Changes in accounts payable	-11,567	-8,839	-12,265	842	9,202
Changes in other liabilities	10,421	148	10,077	243	1,765
Cash flow from operating activities	**-35,849**	**-16,735**	**-33,922**	**-61,079**	**-82,009**
INVESTING ACTIVITIES					
Cash flow from investing activities	**-**	**-**	**-**	**-**	**-**
FINANCING ACTIVITIES					
New share/Warrants issue	-	655	91,258	655	655
Cost new share issue	-	-	-4,323	-	-
Repayment of lease liability	-54	-	-162	-	-
Cash flow from financing activities	**-54**	**655**	**86,774**	**655**	**655**
Cash flow for the period	**-35,903**	**-16,080**	**52,851**	**-60,424**	**-81,355**
Balance at beginning of period	319,549	267,053	229,876	309,531	309,531
Change in cash	-35,903	-16,080	52,851	-60,424	-81,355
Exchange rate difference in cash	3,102	-705	4,021	1,161	1,700
CASH BALANCE AT THE END OF THE PERIOD	**286,748**	**250,267**	**286,748**	**250,267**	**229,876**

*predominantly revaluation of bank accounts in foreign currency

Note: (**1**) Q3 2019 report

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Shareholder list

Shareholders

Source: Monitor by Modular Finance. Compiled and processed data from various sources, including Euroclear, Morningstar and the Swedish Financial Supervisory Authority (Finansinspektionen). The verification date may vary for certain shareholders.

10 largest shareholders

Name	Capital	Votes	Num. of shares	Verified
Staffan Persson	21.11%	21.11%	11 303 314	2019-09-30
Peter Lindell	13.30%	13.30%	7 117 379	2019-09-30
Fjärde AP-fonden	5.98%	5.98%	3 200 000	2019-09-30
Avanza Pension	3.75%	3.75%	2 010 041	2019-09-30
Nordnet Pensionsförsäkring	3.13%	3.13%	1 675 828	2019-09-30
Thomas Eldered	1.69%	1.69%	905 144	2019-09-30
Carl Rosvall	1.55%	1.55%	831 999	2019-09-30
Alfred Berg Fonder	1.31%	1.31%	700 534	2019-09-30
Thord Wilkne	1.31%	1.31%	700 000	2019-09-30
Handelsbanken Fonder	1.30%	1.30%	697 591	2019-09-30
Total 10	**54.44%**	**54.44%**	**29 141 830**	
Total number of owners	3,774			2019-09-30
Total number of shares	53,533,321			2019-09-30

 Source: Nov 2019 Holdings.com

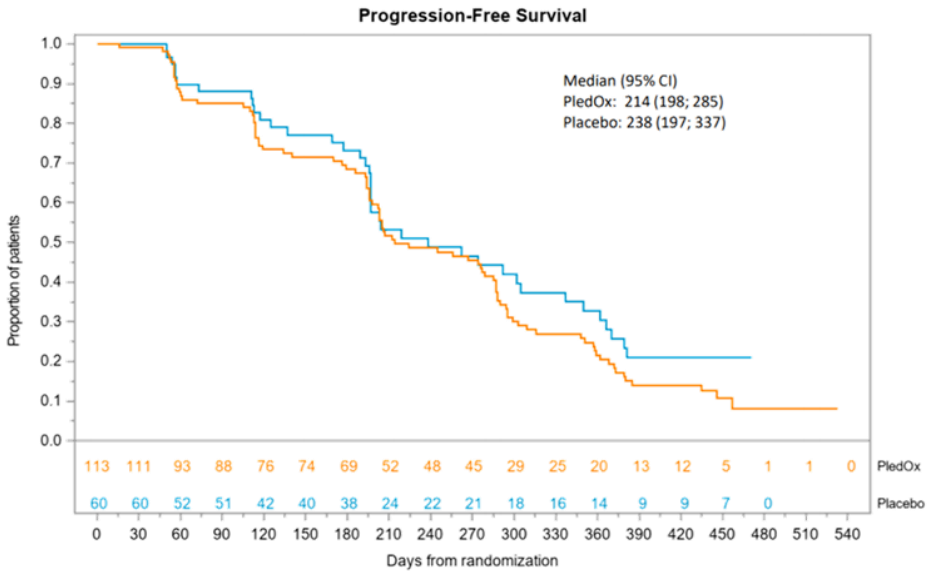
Summary of key neuropathy efficacy endpoints in Phase IIb PLIANT study

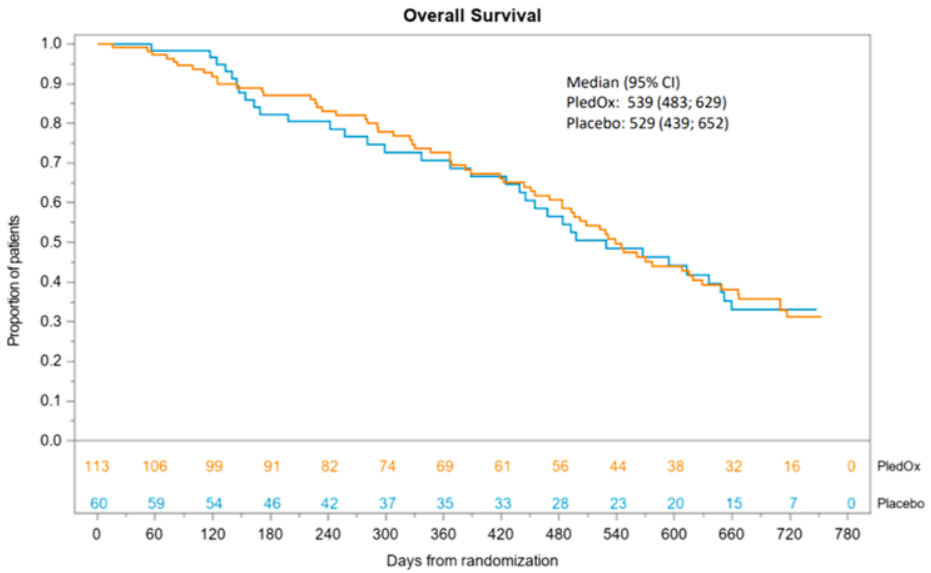
PLIANT study: 173 patients with metastatic CRC treated with PledOx® or placebo together with chemotherapy FOLFOX (oxaliplatin)

Type of CIPN assessment	Dose vs Placebo (Study Part†)	2 µmol/kg (2a+2b)	5 µmol/kg (2b)	2+5+10 µmol/kg (2a+2b)
Physician reported (primary endpoint)	**OSSS odds ratio over cycle 1 to 8§ (nominal p-value)**	0.78 (p=0.31)	0.68 (p=0.25)	0.62 (p=0.16)
Patient reported	**Leonard PRO, odds ratio at FU2* (exploratory analysis; nominal p-value)**	0.38 (p=0.15)	0.12 (p=0.018)	0.23 (p=0.014)

† In the initial part of the study, Part 2a, randomized patient to Placebo, 2 µmol/kg or 10 µmol/kg. After changing the high dose from 10 µmol/kg to 5 µmol/kg, the majority of patients were randomized to Placebo, 2 µmol/kg or 5 µmol/kg in Part 2b.
§ Investigator reported neuropathy grade 2 or higher vs. placebo
* Proportion of patients scoring 3 or more on either numbness, tingling or burning pain/discomfort with cold in hands or feet at FU2 (6 months after last dose), which is approximately 10 months after first dose for the majority of patients that reported follow-up 2.

Progression free survival (PFS) and Overall survival (OS) from Phase IIb study (PLIANT)





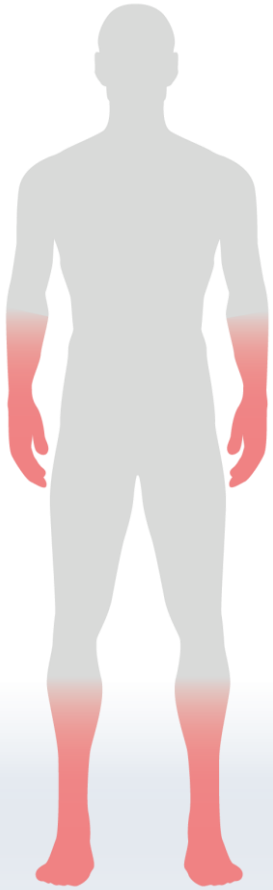
Comment

- No detrimental effect of PledOx® on the anti-tumor effect (PFS) of chemotherapy

Comment

- No detrimental effect of PledOx® on the anti-tumor effect (OS) of chemotherapy

The basis for evaluation of CIPN in the POLAR program



Primary Endpoint	Description
FACT/GOG-NTx-4	4-question PRO instrument addressing key CIPN symptoms of numbness, tingling and discomfort in hands and feet

Secondary & Exploratory Endpoints	Description
FACT/GOG-NTx-13	13-question PRO instrument addressing CIPN broadly
Graduated tuning fork	Objective measure of CIPN
Grooved PEG board	Functional measure of CIPN
Cold sensitivity questionaire	4-question PRO instrument adressing acute CIPN symptoms during chemotherapy
Numeric rating scale of pain	3-question PRO instrument of pain
EQ-5D-5L	General Quality-of-Life PRO instrument

Primary endpoint based on FACT/GOG-Ntx is clinically relevant and interpretable

FACT/GOG-Ntx (4 item)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
NTX 1	I have numbness or tingling in my hands	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet	0	1	2	3	4
NTX 3	I feel discomfort in my hands	0	1	2	3	4
NTX 4	I feel discomfort in my feet	0	1	2	3	4

FACT/GOG-NTx-4 captures the majority of relevant chronic CIPN symptoms

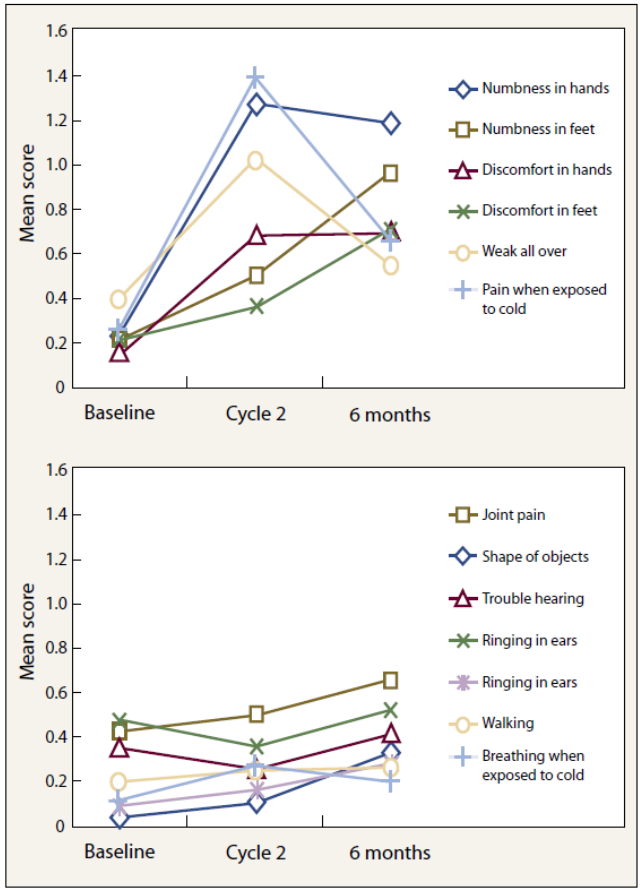


Figure 1 Response Patterns to Neurotoxicity Scale Items

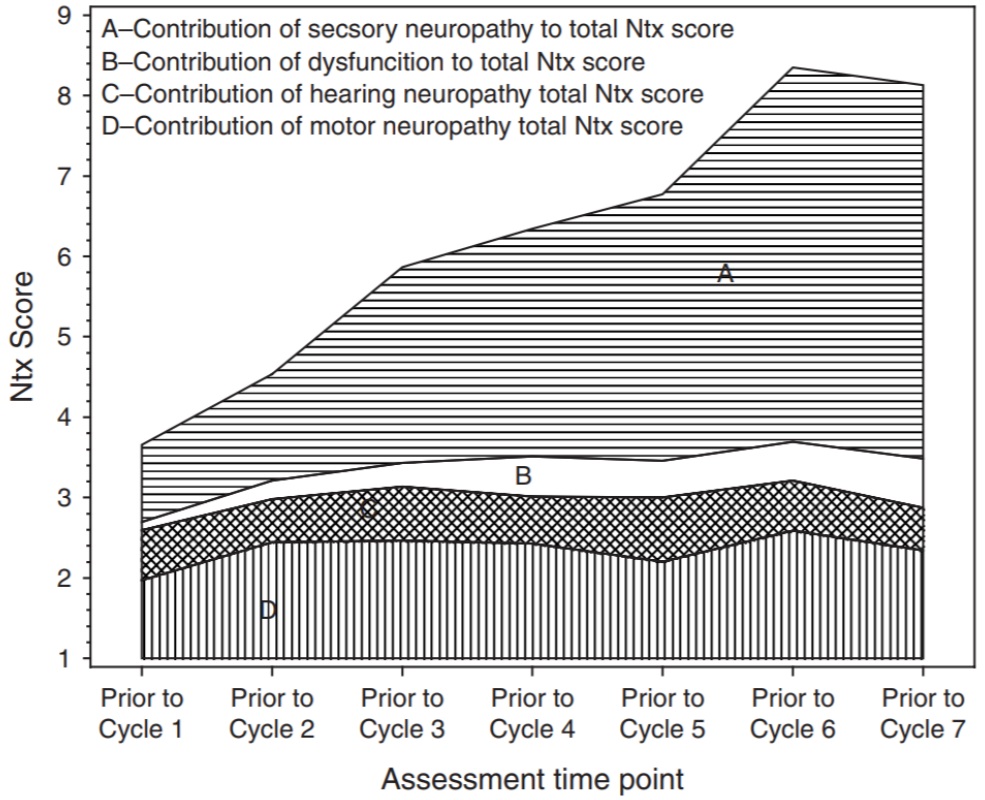


Figure 3. Responsiveness of Ntx scores to TAP cycles received.

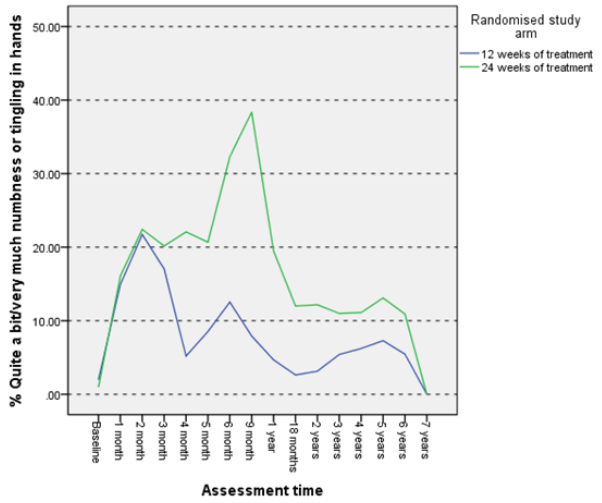
Note: “A” in Figure refers to the questions in Ntx-4

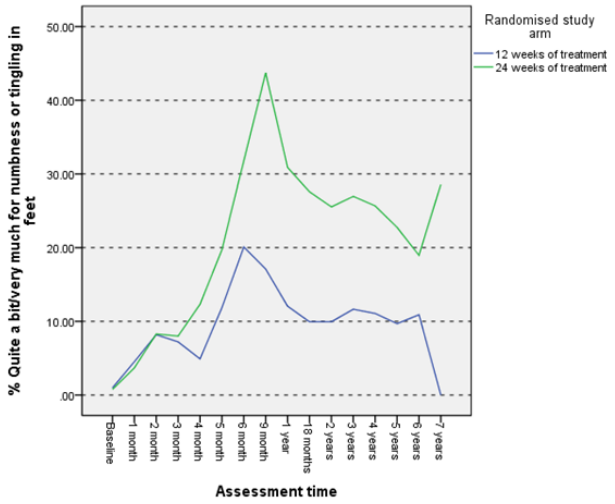
(1) Kopec et.al (2006) Validation of a self-reported neurotoxicity scale in patients with operable colon cancer receiving oxaliplatin
(2) Huang et al. (2007) Validation and reduction of FACT/GOG-Ntx subscale for platinum/paclitaxel-induced neurologic symptoms: a gynecologic oncology group study

Results in SCOT study confirm the sensitivity of FACT/GOG-Ntx-4 in CRC patients treated with oxaliplatin

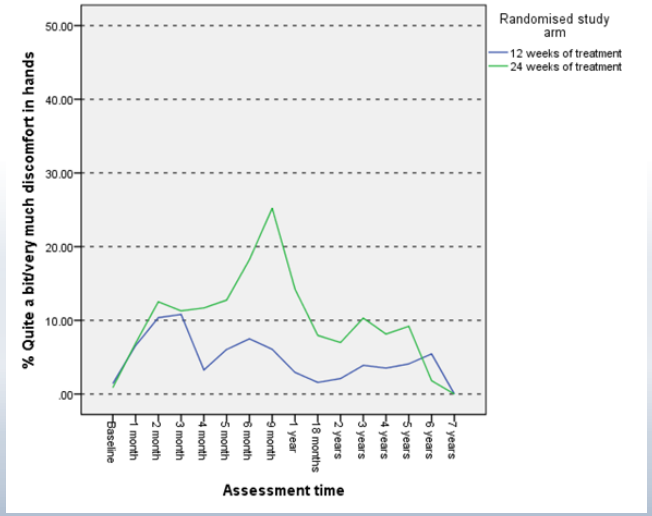
HANDS | **FEET**

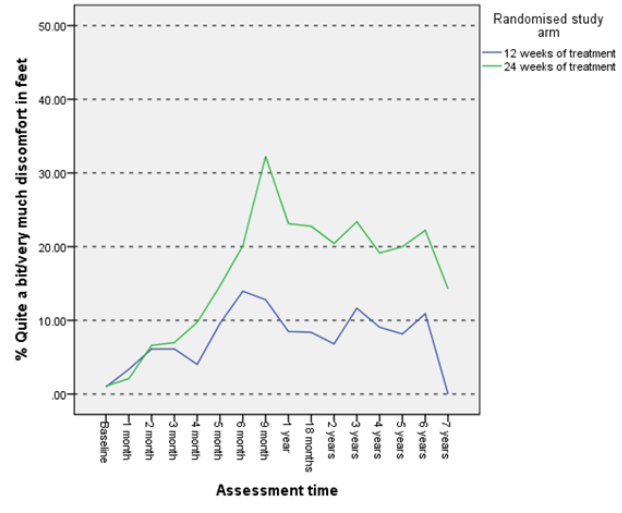
Numbness or tingling





Discomfort





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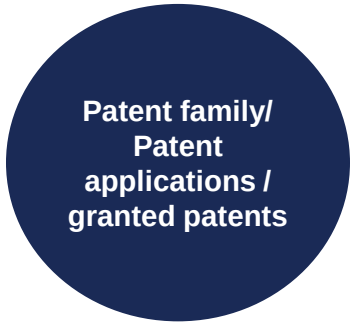
A robust IP portfolio with composition of matter protection until end-2032



- **New chemical entity with composition of matter, manufacturing process and broad therapeutic use of calmangafodipir, with US, EU, China, Russia and Japan approved, end-2032**
- Application for a patent term extension of up to 5 years possible at product registration in major markets (e.g. EU, US and JP)
- Several additional “use” patents for PledOx® and Aladote® such as Cancer treatment methods, 2033, and acute liver failure, 2037.

Trademarks

PledOx® registered trademark in EU, US, Switzerland, Australia, Norway, China, Japan and Russia

Aladote® registered trademark in EU, US, China and Russia

PledOx® is based on a previously used MRI contrast agent, mangafodipir

New compound

Mangafodipir

M = 100% Mn^{2+}

Calmangafodipir

M = 80% Ca^{2+} and 20% Mn^{2+}

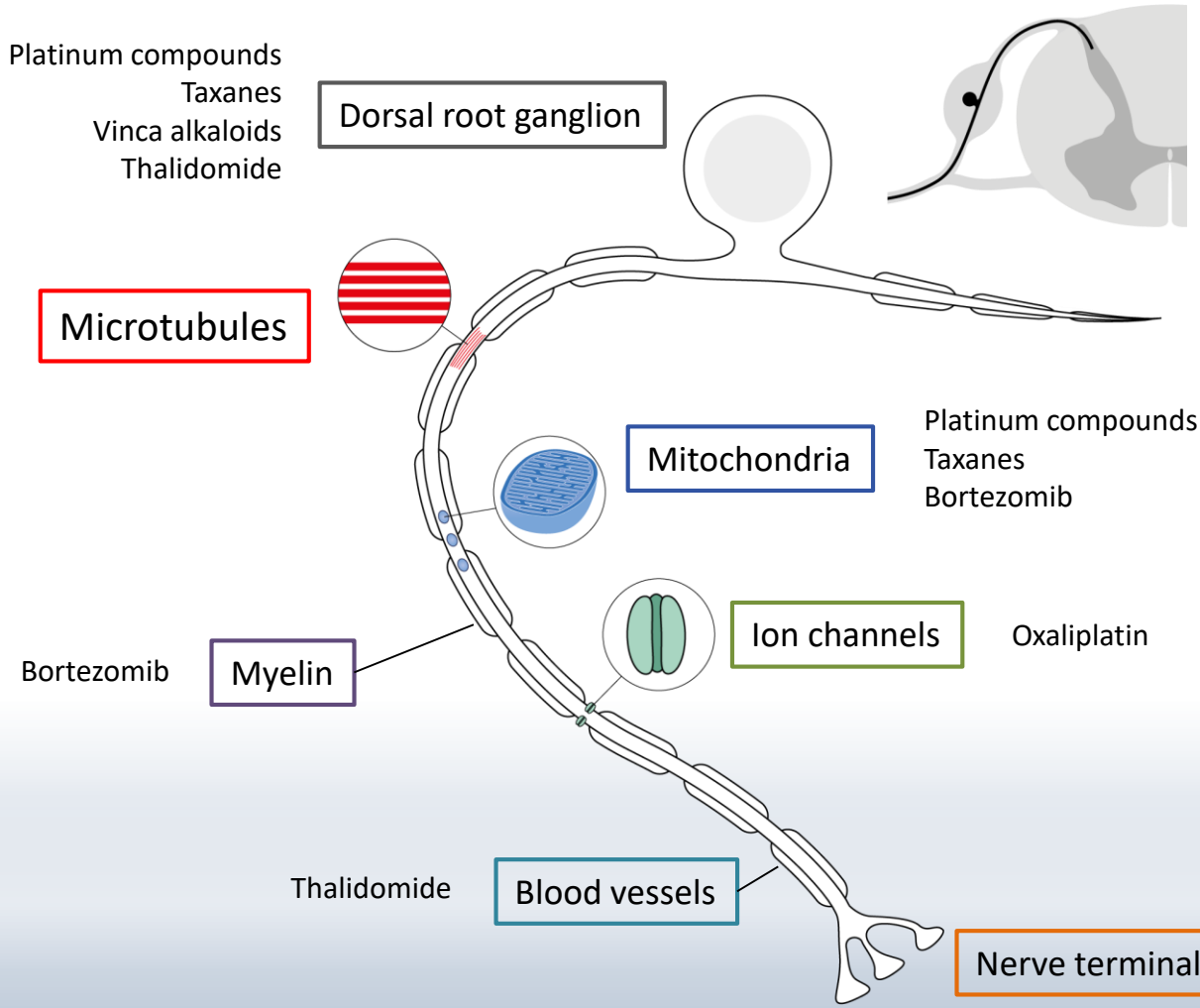
Comments

- Clinically proven MRI contrast medium with good safety profile
- >240,000 patients treated and several toxicity studies
- Mangafodipir has been discontinued
- Anti-oxidative effect of mangafodipir led to compound being tested for therapeutic use

Comments

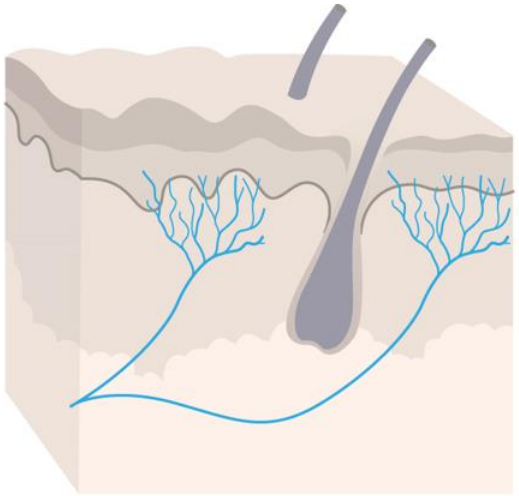
- Mangafodipir's potential for manganese accumulation lead to modification into calmangafodipir
- Significantly more potent and safer than mangafodipir
- Provides for composition of matter patent, granted until the end of 2032

Mechanisms underlying CIPN are diverse and complex

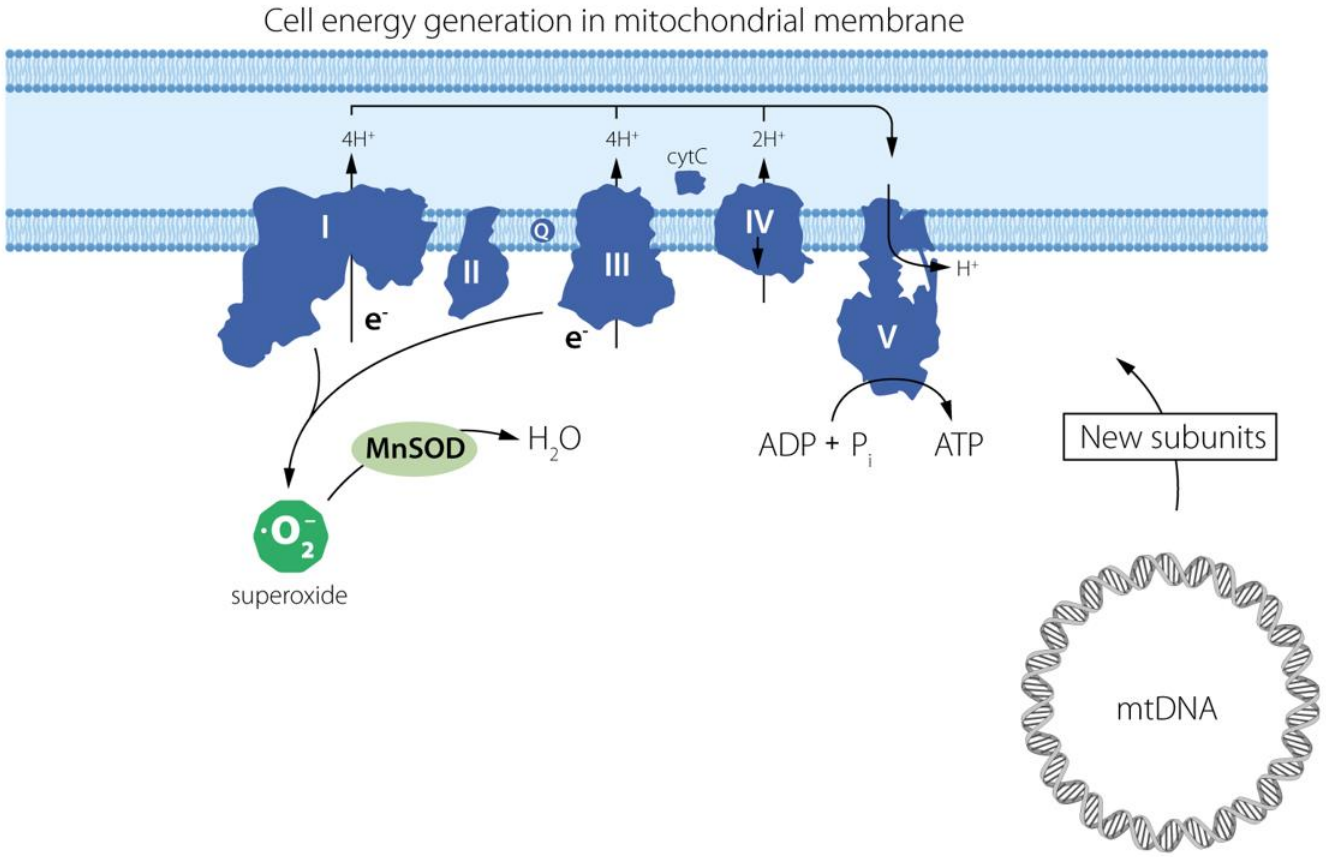


Kerckhove et.al (2017) Long-Term Effects, Pathophysiological Mechanisms, and Risk Factors of Chemotherapy-Induced Peripheral Neuropathies: A Comprehensive Literature Review
Park et al (2008) Mechanisms underlying chemotherapy-induced neurotoxicity and the potential for neuroprotective strategies

In healthy cells, mitochondrial homeostasis is maintained by MnSOD

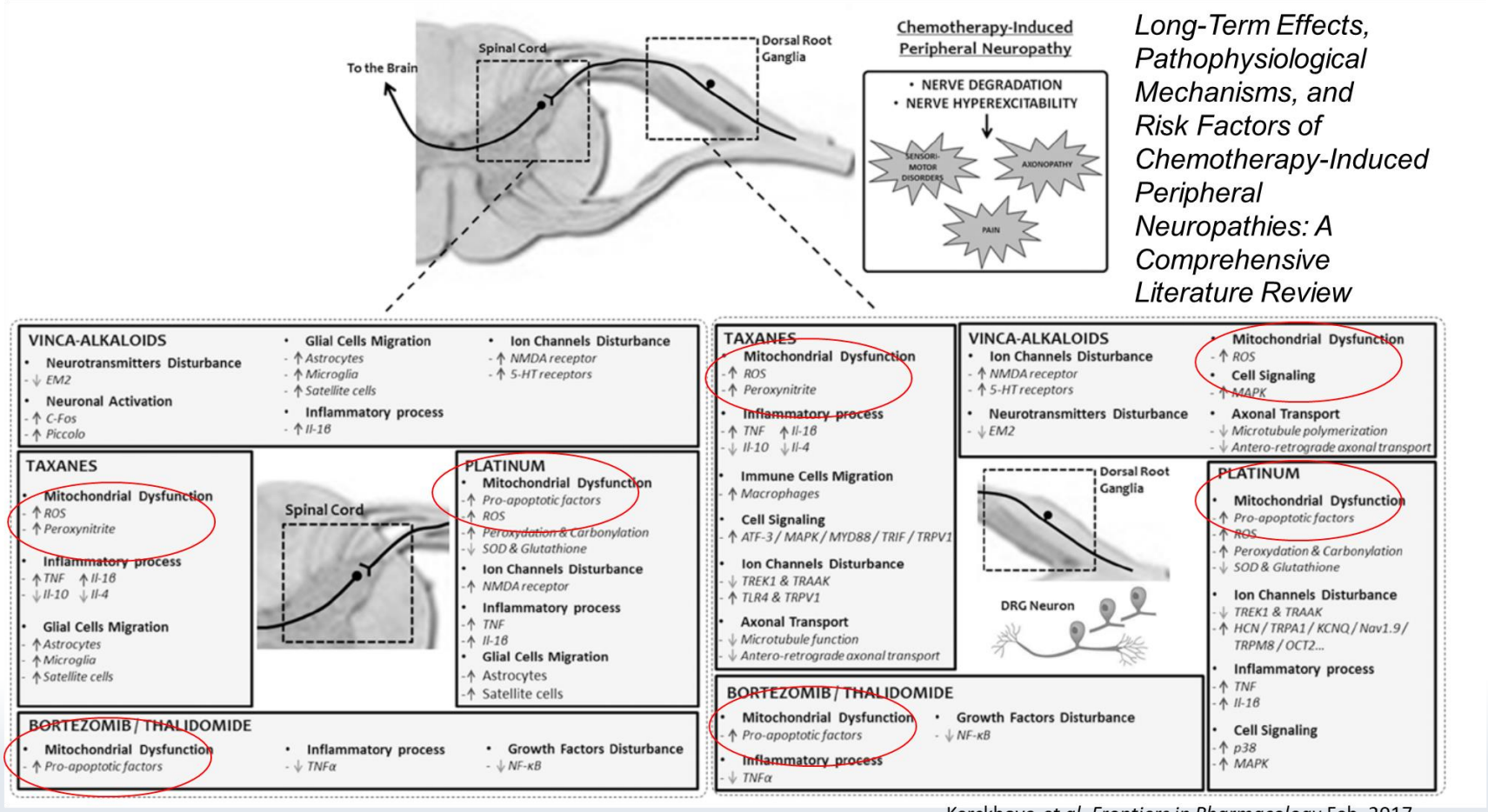


Functional sensory peripheral nerve



- Superoxide is generated as a by-product of energy production in the mitochondria
- MnSOD is an enzyme catalysing the degradation of superoxide

Chemotherapy effect on the mitochondria



Long-Term Effects, Pathophysiological Mechanisms, and Risk Factors of Chemotherapy-Induced Peripheral Neuropathies: A Comprehensive Literature Review

Kerckhove *et al. Frontiers in Pharmacology* Feb, 2017

Comments

Chemotherapy anticancer drugs, such as platinum-based compounds, taxanes, vinca alkaloids, all generate chemotherapy induced peripheral neuropathy (CIPN).
- CIPN is frequently seen as a side-effect in cancer patients,
- Mitochondrial dysfunction mainly in the Peripheral Nervous System, but also the spinal cord, is a suggested mechanism for generating CIPN by all these different classes of chemotherapies.
- CIPN manifests itself as a loss of sensation (numbness) and/or tingling in hands and feet due to the peripheral nerve degradation and hyperexcitability induced by these drugs.

CRC Stage IV (and III) Phase 3 Clinical development landscape

1L mCRC

KEYTRUDA [pembrolizumab]
(PD-1; Merck)

- Active, Not Recruiting: 1L dMMR or MSI-H mCRC; n=308 (May 2018)
- Primary completion: August 2019
- Treatment: Keytruda vs. Investigator Choice SOC (SOC regimens may include [FOLFOX or FOLFIRI] +/- targeted tx)

KEYTRUDA granted FDA accelerated approval for 2L mCRC in 2017

TECENTRIQ [atezolizumab]
(PD-L1; Roche)

- Recruiting: 1L dMMR or MSI-H mCRC
- Primary completion: April 2022
- Treatment: Tecentriq vs. Tecentriq + FOLFOX + Avastin vs. FOLFOX + Avastin

Trial sponsored by National Cancer Institute

2L mCRC

Masitinib
(MEK; AB Science)

- Terminated: 2L mCRC
- Terminated due to Sponsor portfolio prioritization
- Treatment: Masitinib + FOLFIRI vs. FOLFIRI

Encorafenib +/- Binimetinib
(Raf Kinase +/- MEK; Array)

- Active, Not Recruiting: 2L or 3L BRAF V600E+ mCRC
- Primary completion: July 2019
- Treatment: Encorafenib + Erbitux +/- binimetinib vs. Investigator's Choice SOC (SOC may be [FOLFOX + Erbitux] or [Erbitux + irinotecan])

Napabucasin
(STAT3; Boston Biomedical)

- Recruiting: 2L mCRC
- Primary completion: June 2020
- Treatment: Napabucasin + FOLFIRI +/- Avastin vs. FOLFIRI +/- Avastin

3L mCRC

TECENTRIQ (atezolizumab) +/- COTELLIC (cobimetinib)
(PD-L1 +/- MEK; Roche)

- Completed: 3L mCRC
- Primary completion: March 2018. Study completion in Dec 2018, with results March 2019
- Treatment: Tecentriq +/- Cotellic vs. Stivarga

Other

Adjuvant

TECENTRIQ (atezolizumab)
(PD-L1; Roche)

- Recruiting: Adjuvant Stage III dMMR CRC
- Primary completion: December 2020
- Treatment: Tecentriq + FOLFOX vs. FOLFOX

Trial sponsored by National Cancer Institute

Maintenance

Lefitolimod
(TLR9; Mologen AG)

- Active, Not Recruiting: Maintenance mCRC
- Primary completion: March 2019
- Treatment: Lefitolimod vs. Investigator's Choice SOC Maintenance Tx

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Aladote®: About biomarkers

ALT
Alanine transaminase (ALT) is a transaminase enzyme also called alanine aminotransferase (ALAT). ALT is found in plasma and in various body tissues especially the liver's hepatocytes. Serum ALT is commonly measured clinically as part of a diagnostic evaluation of hepatocellular injury, to determine liver health. However, ALT has sub-optimal sensitivity and specificity particularly early after paracetamol overdose. Reference: K. Al-Hourani et al. Q J Med 2013; 106:541–546

Keratin-18 (K18)
In paracetamol overdose, the full-length variant of K18 is released by necrotic cell death. A shorter, caspase cleaved form of K18 is released following cell apoptosis (programmed cell death). Both forms of K18, measured in the first serum sample at presentation at the hospital after paracetamol overdose, correlate with peak ALT activity during the hospital stay. Full length K18 distinguished patients with and without acute liver injury at an early time where ALT activity was still normal. This is consistent with necrosis being more prominent than apoptosis in the pathophysiology of paracetamol-induced acute liver injury.
References: JW Dear et al. Lancet Gastroenterol Hepatol 2018; 3: 104–13; ADB Vliegenthart et al. Br J Clin Pharmacol. 2015; 80: 351–362.

microRNA-122 (miR-122)
miR-122 is a biomarker specific for liver injury and fully conserved (translational) across in vitro models, in vivo models and humans. MiR-122 is an early marker for acute liver injury which predicts a rise in ALT activity following paracetamol overdose. When miR-122 was measured at hospital presentation after a paracetamol overdose in patients requiring subsequent NAC therapy the circulating miR-122 concentration correlated significantly with peak hospital stay ALT activity. MiR-122 was significantly higher in those patients who developed subsequent acute liver injury. miR-122 can accurately separate patients with and without acute liver injury at an early time when ALT activity was still normal. This is consistent with miR-122 having enhanced sensitivity and specificity in this context of use.
References: JW Dear et al. Lancet Gastroenterol Hepatol 2018; 3: 104–13; ADB Vliegenthart et al. Br J Clin Pharmacol. 2015; 80: 351–362.