What a Relief!
EUA declined – US commercial & listing plans started

Relief Therapeutics is a Swiss biopharmaceutical company focused on the development and commercialization of treatments for serious respiratory disorders and rare diseases. Key driver is aviptadil (branded RLF-100™ and ZYESAMI™ in the US), a first-in-class vasoactive intestinal peptide (VIP) with predominant biological activity in the lungs, targeting: 1) COVID-19 induced acute respiratory distress syndrome (ARDS); 2) prevention COVID-19 related ARDS 3) non-COVID-19 related ARDS; 4) pulmonary sarcoidosis, with blockbuster peak sales potential, and 5) checkpoint inhibitor pneumonitis (CIP). In March 2021, Relief added ACER-001, which is aimed at rare diseases such as urea cycle disorders (UCDs), with a 5 June 2022 PDUFA date, and maple syrup urine disease (MSUD). The acquisition of privately held Applied Pharma Research (APR) transformed Relief into a fully integrated biopharmaceutical company from a development-stage company, further diversifying the product offering with in-market products and pipeline projects including Golike for phenylketonuria (PKU) and APR-TD011 in development for epidermolysis bullosa (EB). The FDA decline to grant US Emergency Use Authorization of RLF-100 IV in critical COVID-19 patients in November 2021 pushes back a potential US approval by roughly a year upon positive ACTIV-3b trial results in Q4 2022. CHF 45 mn cash provides funding into late 2023. We derive a sum-of-parts rNPV of CHF 0.520/share and qualify the risk profile as Speculative with no substantial revenues, yet.

Key catalysts:
1) Start phase IIb trial RLF-100 INHALED in pulmonary sarcoidosis (H1 2022): important non-COVID-19 indication with few treatments. Our success rate increases to 50% (phase II dose ranging) from 35% increasing the rNPV by CHF 0.021/share.
2) “AVICOVID-2™ results RLF-100 INHALED in prevention COVID-19 related ARDS (H1 2022): Additional COVID-19 indication for RLF-100. Our rNPV increases by CHF 0.015/share with a 72.5% (average US 80% filing and EU 65% phase III) success rate on positive topline results.
3) PDUFA date ACER-001 in urea cycle disorders (5 June 2022): Our rNPV for RLF-100 IV increases by CHF 0.005/share with a 90% success rate (average assuming US approved (100%) and EU filed (80%))
Recent Developments

Since our last Relief Therapeutics Valuation Report in October 2021, US partner NRx Pharmaceuticals (formerly NeuroRx) announced that the FDA declined to grant Emergency Use Authorization (EUA) for RLF-100 IV in critical COVID-19 patients with respiratory failure in the US, citing insufficient data to establish a positive benefit/risk. This pushes back a potential US approval for RLF-100 IV in COVID-19 induced ARDS by roughly a year until the NIH sponsored phase III “ACTIV-3b/TEISCO” trial results are announced in Q4 2022. A third positive safety review for this trial was announced by the independent DSMB in November. Despite the setback, Relief remains committed to the development of RLF-100 for the treatment of respiratory complications including COVID-19 infection. The topline results of the phase IIb/III “AVICOVID-2” trial of RLF-100 INHALED in prevention of COVID-19 related ARDS are now expected to report in H1 2022 from previously Q4 2021. Positively, a recent FDA reviews allows for high volume production of RLF-100, while the shelf life has been extended to 150 days from 62. Relief and NRx have agreed to hold a mediation to amicably resolve the ongoing litigation between both parties in early January 2022.

An important formulation (taste-masking) patent for ACER-001 was issued in the US extending patent expiry until 2036. Positive interim results were reported of a post-market trial for APR’s novel nasal spray Sentinox, suggesting it could be effective in reducing time to negativization in COVID-19 infected patients. Sentinox has already been approved in the EU as a Class III Medical Device.

Relief’s Level 1 ADR program was launched in the US under trading symbol “RLFTY” to facilitate US investors. Relief intends to transition its ADR program into a NASDAQ Stock Market listing in H1 2022.

Cash of CHF 45 mn, which together with exercising flexible financing tools, provides a cash runway into late 2023. Relief may need a maximum of CHF 25-30 mn in additional funding to reach positive operating cash flow status before the end of 2024, which is dependent upon timely approval of ACER-001 in the US.

As a result, our sum-of-parts rNPV for Relief declines by 21% to CHF 0.520/share from previously CHF 0.661/share largely due to the FDA declining to grant a EUA for RLF-100 IV in COVID-19 induced ARDS leading to a delay of roughly a year for a potential US approval.

November 18 – Level 1 ADR program launched in the US under ticker “RLFTY”
Relief’s Form F-6 registration statement has become effective, and the company has launched its Level 1 American Depositary Receipt (ADR) program in the US. It is expected that Relief’s ADRs will begin trading on the over-the-counter ("OTC") market on 18 November 2021 under the trading symbol "RLFTY". Relief’s ADR program will complement its existing primary listing on the SIX Swiss Exchange. JPMorgan Chase Bank has been appointed as the depositary bank for the Level 1 ADR program. Each ADR will represent 150 of Relief’s ordinary shares. ADRs allow US investors to buy shares in foreign companies without the need for cross-border or cross-currency transactions. They are priced in US dollars and can be traded like shares of US-based companies in the OTC market. Relief’s goal is to take the necessary steps in the future to transition its ADR program from a Level
1 ADR program to a Level 2 or a Level 3 ADR program, with the ultimate goal of listing its ADRs on the NASDAQ Stock Market during H1 2022.

**November 12 - FDA review RLF-100 Manufacturing Information**

NRx reported the completion of an FDA Manufacturing Information review, without the imposition of any clinical hold, which enables NRx to distribute RLF-100, produced at commercial scale under GMP (Good Manufacturing Practices) for clinical trials and other future purposes. The FDA has now reviewed a GMP manufacturing process at a batch size of 10,000 – 100,000 doses with a current shelf life of 150 days. This new process, helped by Nephron Pharmaceuticals, replaces the handmade, 300 dose batches with a limited shelf life of 62 days. NRx will work together with the FDA to complete CMC (chemistry, manufacturing and controls) review that will be needed for any potential drug approval.

**November 11 – Corporate update to outline plans for diversified pipeline portfolio**

Following the FDA decision to decline a grant for an EUA for RLF-100 IV in critical COVID-19 patients with respiratory failure, Relief provided a corporate update that outlines its plans to advance its diversified portfolio of pipeline candidates, including:

**RLF-100 (aviptadil):** Relief remains committed to the development of this compound for the treatment of respiratory complications, including COVID-19 indications (the treatment and prevention of COVID-19 related ARDS) as well as non-COVID-19 indications such as pulmonary sarcoidosis (phase II trial to start in Germany in 2022), ARDS (acute respiratory distress syndrome), CIP (checkpoint inhibitor-induced pneumonitis) chronic beryllium disease (berylliosis). Relief is also working to optimize the formulation of aviptadil.

**US commercial initiatives:** Relief is focused on establishing its own US commercial operations, headed by newly appointed Anthony Kim, to market its lead commercial product Golike for the treatment of phenylketonuria (PKU). The company is also working close together with Acer Therapeutics on the preparations for a potential launch of ACER-001 in urea cycle disorders (UCDs) with a 5 June 2022 PDUFA date, when the FDA is expected to complete its review. Relief is preparing to submit an MAA (marketing authorization application) to the EU and UK regulatory agencies in H1 2022. Relief also intends to assess a clinical program for ACER-001 in maple syrup urine disease (MSUD) in 2022. Both companies continue to explore strategic options to advance the optimization of ACER-001’s commercial value in territories beyond the US, UK and Europe.

**Other Initiatives:** Relief intends to advance APR-TD011 for epidermolysis bullosa (EB), a billion US dollar annual target market according to Knowledge Sourcing Intelligence. Relief believes that APR-TD011 could prove a transformative solution for EB patients, who suffer from debilitating pain due to large, chronic, constantly blistering skin wounds. APR-TD011 could improve the quality of life of EB patients by accelerating wound healing and reducing the itching and pain linked to infections and inflammation. Relief also possesses an array of other assets acquired from APR, including: **Sentinox**, a novel nasal spray solution for upper airway infections with viral pathogens including the SARS-CoV-2 virus, the causal agent of COVID-19 (positive interim data was recently reported, approved in the EU as a Class III Medical Device); **Nexodyn AOS**, an acid-oxidizing solution for treatment of chronic wounds (including...
foot ulcers); and the PHYSIOMIMIC platform-enabled amino acid-based product candidates for an array of rare metabolic disorders.

**Capital Resources:** With cash of CHF 45 mn, Relief expects that it has sufficient resources to fund operations into late 2023. Relief also expects that with a successful launch of ACER-001 and the potential expansion of the Golike franchise into the US, positive operating cash flow could occur during 2024. A maximum of CHF 25-30 mn in additional funding may be needed to reach positive operating cash flow status before the end of 2024. This could also be positively affected if Relief is successful in obtaining an approval to market RLF-100.

**November 9 – Management transitions to prepare for upcoming launches**
Effective 1 December 2021, Anthony M. Kim, a seasoned biotech executive with vast US commercial launch experience, will be appointed Senior Vice President and Head of US Commercial Operations, to spearhead Relief’s US commercial operations starting with the launch of Golike in phenylketonuria (PKU). Chris Stijnen, Chief Commercial Officer since 2020, will be leaving Relief to pursue other opportunities effective 30 November 2021. The European and UK commercial operations will be transitioned to Paolo Galfetti, President of Relief Europe and the commercial team at Relief’s subsidiary APR.

**November 4 – FDA declines EUA for RLF-100 IV in COVID-19 related ARDS**
NRx reported that the FDA declined to issue Emergency Use Authorization (EUA) for RLF-100 IV for the treatment of acute respiratory failure due to critical COVID-19. This is the second time the FDA declined EUA for RLF-100 IV (previously in December 2020). The FDA stated that it was unable to issue the EUA at this time due to insufficient data regarding the known and potential benefits of the medicine and the known and potential risks of RLF-100 IV in patients suffering from critical COVID-19 with respirator failure. In its letter, the FDA noted that so far, it has reviewed safety in only 131 randomized patients treated with RLF-100 IV. NRx states that it will attempt to coordinate a review by the FDA of the 150 or more additional patients already treated with RLF-100 IV in the NIH-sponsored ACTIV-3b/TESICO trial. The trial has enrolled more than 300 patients of the targeted 640 patients with three positive safety reviews by the independent DSMB. According to clinicaltrials.gov, the primary completion date of the ACTIV-3b/TESICO trial is October 2022, when topline results should be reported. We do not fully understand how NRx will attempt a review by the FDA of the more than 150 patients enrolled as the trial is still actively enrolling and blinded, which would compromise the final results. Therefore, we believe the filing of a new US EUA can only occur after the topline results of the ACTIV-3b/TESICO have been announced in Q4 2022, leading to roughly a year’s delay for a potential US approval for RLF-100 IV in treating COVID-19 related ARDS.

**November 3 – First steps taken for US public listing of Relief Therapeutics**
Relief has taken the first steps to establish a Level 1 American Depositary Receipt (ADR) program in the US by filing a registration statement on Form F-6 with the US Securities and Exchange Commission. The ADRs have started trading on the OTC market on 18 November 2021 under the trading symbol "RLFTY" (see above).

**November 3 – “ACTIV-3b/TESICO” trial to continue after no safety concerns**
A third positive safety review was reported for the ongoing “ACTIV-3b/TESICO” (Therapeutics for Severely Ill Inpatients with COVID-19) critical care phase III trial sponsored by the US National Institutes of Health. The trial is designed to evaluate RLF-100 IV and
Gilead’s Veklury (remdesivir) in critical COVID-19 patients, as a monotherapy and in combination against placebo. The trial's independent Data Safety Monitoring Board (DSMB) found no new safety concerns after reviewing a total of more than 300 patients and recommended continued enrollment to target 640 patients.

October 27- Positive interim results confirm early safety and efficacy of Sentinox
Positive interim results were reported from a post-market clinical trial of nasal spray Sentinox in SARS-CoV-2 infected patients, confirming its safety and tolerability. The data from the trial suggest that Sentinox could be effective in reducing the SARS-CoV-2 viral load at the level of the nasal mucosa. Consequently, the use of Sentinox could help reduce the transmissibility of the virus and, consequentially, its spread.

The post-market, confirmatory, interventional, randomized, placebo controlled clinical trial is expected to enroll a total of 57 patients. The trial is designed to assess the efficacy and safety of Sentinox spray in reducing viral load in the upper respiratory airways of recently infected SARS-CoV-2 individuals and is being conducted in Genoa, Italy. The interim analysis, based on 30 patients who have completed the trial - 10 patients for each treatment group (0.5 ml into each nostril, 3x/day, 5x/day or control group, for five days) - showed that all patients treated with Sentinox tested negative for SARS-CoV-2 by the end of the study period (Day 21). By contrast, one out of 10 patients in the control group was still positive by Day 21. All subjects using Sentinox 3 times a day had already tested negative by visit number 7 (V7; Day 10) vs. 70% of subjects in the control group over the same study period. At visit 4, 5 and 6, a trend in favor of the 3 times a day treated group vs. control group was observed (10% of patients using Sentinox tested negative at V4 vs 0% of patients in the control arm; 40% of patients using Sentinox tested negative vs 20% in the control arm at V5; 70% of patients using Sentinox tested negative vs 40% at V6). For the purpose of this study, subjects are considered negative when their COVID-19 test becomes negative and remains negative throughout the study period. Topline results of the trial are expected to report in 2022.

October 26 – New US ACER-001 formulation patent provides protection up to 2036
The US Patent and Trademark Office (USPTO) has issued a new US patent to Acer for certain claims related to ACER-001 (sodium phenylbutyrate). Patent 11,154,521 covers pharmaceutical composition claims related to ACER-001’s taste-masked, multi-particulate dosage formulation for oral administration. The newly issued patent provides protection up to 2036 in the US. Relief plans to submit the patent for listing by the US FDA in its Approved Drug Products with Therapeutic Equivalence Evaluations, or so-called “Orange Book”, should ACER-001 receive marketing approval. Acer and Relief are pursuing similar claims in the European Patent Office (EPO) to cover ACER-001 and plan to submit a Marketing Authorization Application (MAA) for ACER-001 for the treatment of patients with UCDs in the EU in Q2/Q3 2022.
Strategy & Cash Position

Providing patients therapeutic RELIEF from serious diseases with high unmet need
Relief Therapeutics Holding SA (Relief) was formed in 2016 following the reverse merger of Relief Therapeutics SA, which was founded in 2013 as a private company by three former Merck Serono executives, and THERAMetrics Holding AG (formerly mondoBIOTECH Holding AG, which was founded in 2007 and listed on the SIX Stock Exchange in 2009). Relief is a Swiss biopharmaceutical company focused “on providing patients with therapeutic RELIEF from serious diseases with high unmet medical need”. Development activities of the company focus primarily on clinical-stage projects based on molecules of natural origins (e.g., peptides and proteins) with a history of clinical testing (benign safety and tolerability) and use in human patients (proof-of-concept) or a strong scientific rationale with a special focus on respiratory and rare disease.

To strengthen and expand its pipeline, Relief signed a collaboration and license agreement with Acer Therapeutics (symbol: ACER), based in Newton, Massachusetts, USA, in March 2021, for the worldwide development and commercialization of ACER-001 for the treatment of rare diseases. In June 2021, Relief acquired the privately held Applied Pharma Research (APR), based in Balerna, Switzerland with sales and marketing subsidiaries in Rome, Italy, and Offenbach, Germany, which transformed Relief in a fully integrated commercial-stage biopharmaceutical company from a development-stage company. Relief’s headquarters is based in Geneva, Switzerland and currently has ~50 employees following the APR acquisition. Relief will strategically grow the management team as the company evolves (for Management and Board biographies see page 64).

Relief’s primary listing is on the SIX Swiss Stock Exchange (symbol: RLF) with an additional listing on the OTC Markets at OTCQB (symbol: RLFTF). In November 2021, Relief’s Level 1 ADR program was launched in the US under trading symbol “RLFTY” to facilitate US investors. Relief intends to transition its ADR program into a NASDAQ Stock Market listing in H1 2022.

Strategy to reposition RLF-100™ in respiratory disease, expand its product offering through APR acquisition and develop & commercialize ACER-001 in rare diseases
Relief’s focus is the clinical development and commercialization of its key pipeline project aviptadil (designated RLF-100™ and branded under the trade name ZYESAMI™ in the US) in new treatment solutions for respiratory disease. The APR acquisition brings to Relief a pipeline of product candidates at various stages of development, including marketed products, near-to-market products, and a varied clinical development portfolio that offers exciting growth opportunities, with multiple synergies across Relief’s pipeline projects. With APR’s emerging commercial platform, Relief obtains a springboard for rolling out marketed products and a base for future product launches in Europe, providing a strong and evolving foundation extending beyond the company’s current lead programs, RLF-100 and ACER-001, a late-stage compound for the rare diseases urea cycle disorders (UCDs) with a potential launch in 2022 and maple syrup urine disease (MSUD) in 2023, both with a high margin potential. Relief will continue to search for additional strategic acquisitions to further strengthen its pipeline.
RLF-100 has a promising profile to repurpose for respiratory disease

RLF-100 is a direct analog of vasoactive intestinal polypeptide (VIP), which was acquired from mondoBIOTECH. This legacy compound was originally developed in combination with phentolamine mesylate and has been marketed in Europe since 1998 for the treatment of erectile dysfunction. RLF-100 is a synthetic form of VIP, an abundant biologically active endogenous human peptide that possesses anti-proliferative, anti-inflammatory, and immune-regulatory activities. Its predominant biological activity is observed in the lung. Hence, Relief's plan to repurpose RLF-100 for respiratory disease.

RLF-100 obtained Investigational New Drug (IND) clearance from the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for phase II clinical trials in acute respiratory distress syndrome (ARDS), a type of respiratory failure characterized by rapid onset of widespread inflammation in the lungs often caused by sepsis, infection, pancreatitis, trauma, pneumonia and aspiration, with a lack of effective treatments and a poor outcome with a mortality rate ranging between 35% and 50%. RLF-100 has been granted orphan drug designation (ODD) by both agencies for acute lung injury (ALI) including ARDS, and sarcoidosis, a rare disease caused by inflammation, particularly in the lungs with limited treatment options. Orphan drug designation (ODD) provides 7 years (US) and 10 years (EU) of market exclusivity from the approval date.

Change in priority after rapid arrival COVID-19 pandemic and early proof of efficacy

Relief's initial plans were to develop RLF-100 for pulmonary sarcoidosis. However, with the rapid arrival of the COVID-19 pandemic in early 2020, the company decided to repurpose the use of the RLF-100 to protect the lung from injury caused by COVID-19 infection. RLF-100 is believed to be the first COVID-19 therapeutic to demonstrate the ability to block replication of the COVID-19 virus in human lung cells and monocytes, while also preventing synthesis of cytokines in the lung and protecting the vulnerable type II alveolar cells. Early results from an ongoing US open label Expanded Access Program (EAP) dubbed “SANICARE” in 2020 demonstrated a 72% survival rate for patients given RLF-100 on top of best standard of care in critically ill COVID-19 patients with respiratory failure who were admitted to the intensive care unit (ICU).

Consequently, the company's priority changed to rapidly develop RLF-100 as treatment of COVID-19 induced acute respiratory distress syndrome (ARDS), a major complication of COVID-19 infection with a lack of effective treatments resulting in a high mortality rate, and for the prevention of COVID-19 related ARDS in hospitalized patients with moderate to severe COVID-19. Thanks to the global rollout of effective coronavirus vaccines, the SARS-CoV-2 pandemic is expected to become endemic in the coming years with occasional flare-ups. In particular, the continual emergence of new coronavirus variants that may be immune or more resistant to current vaccines pose a continued risk. Therefore, the need for new safe and effective treatments for COVID-19 patients is expected to persist.

RLF-100 is available in two different formulations with clinical development plans for four respiratory indications:

1. **IV formulation**: RLF-100 IV is an intravenous (IV) injection formulation of aviptadil developed for use in a healthcare setting to treat acute respiratory diseases. RLF-100 IV key indications include:
   - **COVID-19 induced ARDS** (peak sales CHF 200+ mn – EUA declined): ongoing US open label Expanded Access Program (EAP) “SAMICARE” trial
showed a 72% survival rate for RLF-100 in patients with COVID-19 induced ARDS; FDA Fast Track Designation granted June 2020; US double-blind phase IIb/III “COVID-AIV” trial in 196 COVID-19 induced ARDS patients started June 2020 reported positive 60-day topline results in March 2021; US Emergency Use Authorization (EUA) declined on 4 November 2021, new EUA filing expected in Q4 2022, a grant would be transformational for Relief marking first commercial sales of RLF 100; EUA grant could trigger potential EU Conditional Marketing Authorization (CMA) in H1 2023; RLF-100 IV included into the “I-SPY COVID-19” platform trial assessing multiple experimental drugs in COVID-19 patients as well as NIH-sponsored phase III “ACTIV-3b/TESICO” trial

- **Non-COVID-19 ARDS** (peak sales CHF 450+ mn - phase IIb/III trial is under consideration, but with no clear guidance by the company at this time): clinical development in patients with acute respiratory distress syndrome (ARDS) not caused by COVID-19 but other causes such as sepsis, pancreatitis, trauma or pneumonia; phase IIb/III trial results potentially could come as soon as 2022; sNDA (supplemental New Drug Application) in 2022; US launch 2023, EU launch 2024

2. **Inhaled formulation**: RLF-100 INHALED, is an inhaled formulation of aviptadil developed to be administered locally by a mesh nebulizer, which can be used in the home setting to address chronic respiratory diseases. RLF-100 INHALED key indications, include:


- **Pulmonary sarcoidosis** (peak sales CHF 500+ mn – phase IIb start 2022): initial target indication for RLF-100 before onset of COVID-19 pandemic early 2020; promising POC results published in 2010; phase IIb dose ranging trial to start in 2022; approval and launch expected in 2025; orphan drug designation (ODD) granted in the US in 2007; eligible for 7 years US market exclusivity from date of approval.

**ACER-001**, a novel powder formulation of sodium phenylbutyrate (NaPB) designed to be both taste-masked and immediate release (IR) is targeted for development and commercialization in two rare diseases:

1) **Urea Cycle Disorders (UCDs)**: (peak sales CHF 130+ mn – 505(b)(2) pathway): bioequivalence to Buphenyl obtained under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act; completing additional non-clinical work and 12-month long-term stability data; 5 June 2022 PDUFA date with first launches expected in 2022; potential 3 years Hatch-Waxman market exclusivity; taste-masked formulation US patent issued that protects the compound into 2036; potential to obtain Orphan Drug Designation in the EU providing 10 years market exclusivity; targeted to replace Horizon’s UCDs drugs Buphenyl and Ravicti and attract new and non-compliant sufferers of UCDs

2) **Maple Syrup Urine Disease (MSUD)**: (peak sales CHF 80+ mn – POC established): based on the encouraging POC results a phase IIb/III trial is
planned for 2022; potential US launch in 2023 and EU launch in 2024; obtained Orphan Drug Designation in the US, which provides 7 years market exclusivity; there are currently no drugs approved to treat MSUD

APR acquisition adds marketed, niche and near-market products as well as high margin pipeline projects next to an emerging specialist sales platform

- **Marketed products:** (royalty revenues CHF ~14 mn): main royalty generating products consisting of multiple reformulations of existing drugs, including Cambia and Voltfast for acute migraine, Eminocs for acute pain and Voltadol for local pain and strains; commercialized by partners in return for royalties; several products to phase out in next few years
- **Niche disorders:** (peak sales TBD): including Nexodyin AOS, a sprayable HClO solution for acute and chronic wounds; Setofilm/Zuplenz/Ondissolve, an oral dispersible film containing ondansetron for treating chemotherapy-, radiotherapy- and postoperative nausea and vomiting; Sentinox a ready to market class III medical device sprayable HClO solution to block transmission of SARS-Cov-2 virus, approved in EU in February 2021; APR-TM011 approved in the EU for the prevention and treatment of skin rashes associated with cancer treatments; Relief assessing which products offer the optimal strategic fit combined with differentiation that can offer strong growth potential
- **Golike (phenylketonuria – PKU):** (peak sales CHF 50+ mn): first food for medical purposes (FSMP) engineered with delivery technology with an improved metabolic management and better compliance with minimized taste, odor and aftertaste; complete line of products covering main age groups and individual habits; launched in EU in 2018; US launch likely in H1 2022; US approval as prescription-only treatment could boost peak sales to CHF 200+ mn
- **APR TD-011 (epidermolysis bullosa - EB):** (peak sales CHF 900+ mn): novel HClO sprayable solution with strong antimicrobial and anti-inflammatory properties; US Orphan Drug Designation (ODD) granted Q4 2019 on promising early-stage programs providing 7-years market exclusivity from approval date; potential for EU ODD with 10-years market exclusivity; discussions with regulators ongoing to finalize clinical development path, phase IIb trial to start mid 2022, potential launch in 2025

All set to develop and commercialize RLF-100 in COVID-19 disease and beyond, to develop and commercialize ACER-001 in several rare diseases and to expand product offering through APR acquisition

After a flurry of deals since early 2020, Relief is now preparing to successfully develop, manufacture, distribute and commercialize RLF-100 in COVID-19-induced ARDS, prevention of COVID-19 related ARDS as well as non-COVID-19 ARDS and pulmonary sarcoidosis, develop and commercialize ACER-001 in UCDs and MSUD, and expand its product offering through the APR acquisition with sufficient funding for operations secured into late 2023.

- **Development & Commercialization agreements:**
  - **NRx Pharmaceuticals:** Relief entered into a Collaboration Agreement with NRx Pharmaceuticals (formerly known as NeuroRx Pharmaceuticals) in September 2020. NRx will conduct the clinical trials of RLF-100 in COVID-19 related respiratory disease (e.g., positive US phase IIb/III “COVID-AIV” trial in COVID-19
induced ARDS; US phase IIb/III “AVICOCID-2” trial in prevention COVID-19 related ARDS. NRx will lead commercialization in the US, Canada and Israel, while Relief will be responsible for Europe and ROW. Profits will be split 50/50 in the US, Canada and Israel, while they will be split 85/15 in Europe and 80/20 in ROW, in favor of Relief. Relief is in an ongoing dispute with NeuroRx and its CEO Dr. Javitt, alleging breaches in the Collaboration Agreement for the development and commercialization of Relief’s RLF-100, leading to significant delays. In October 2021, Relief filed a US lawsuit against NeuroRx and its CEO Dr. Javitt. Relief and NRx have agreed to hold a mediation to amicably resolve the ongoing litigation between both parties in early January 2022.

- **Quantum Leap**: NRx signed an agreement to include RLF-100 in the US “I-SPY COVID-19” trial, a platform trial assessing multiple experimental drugs in COVID-19 patients and sponsored by Quantum Leap, a 501c(3) charitable organization. RLF-100 will be included as one of the first drugs targeting respiratory failure in critically ill COVID-19 patients.

- **Syneos Health**: a global clinical research organization (CRO), is expected to run the European phase IIb/III clinical trial of RLF-100 in COVID-19 induced ARDS (if such a study is deemed necessary for approval by European regulators).

- **AdVita Lifescience**: In January 2021, Relief and AdVita signed a binding term sheet for Relief to acquire all shares of AdVita, a privately held German pharmaceutical company, in exchange for EUR 25 mn Relief common shares plus future contingent milestones up to EUR 20 mn, which was successfully closed in July 2021. Relief will gain pending IP rights that may cover RLF-100 INHALED formulation specifications and potential applications of RLF-100 INHALED in ARDS and checkpoint inhibitor-induced pneumonitis (CIP).

- **Acer Therapeutics**: In March 2021, a definitive agreement was signed between Relief and Acer Therapeutics for an exclusive collaboration and license agreement for the worldwide development and commercialization of ACER-001 in urea cycle disorders (UCDs) and maple syrup urine disease (MSUD), both rare diseases with a high margin potential. ACER-001 in UCDs is in late stage of development with launch expected in 2022 and potential peak sales of CHF 130+ mn. Acer received a USD 1 mn non-refundable payment for exclusivity until 30 June 2021 (for the initial option agreement signed in January 2021) and an additional USD 10 mn in cash and will retain development and commercialization rights in the US, Canada, Brazil, Turkey and Japan, with a 60% profit split in favor of Relief. Acer will receive 15% net sales royalties from Relief for ROW sales and a total of USD 6 mn milestones based on the first EU marketing approvals of ACER-001 in UCDs and MSUD. Relief will pay up to USD 20 mn in US development and commercial launch costs for the UCDs and MSUD indications, of which USD 15 mn has been paid to-date.

- **TFF Pharmaceuticals**: In March 2021, US partner NRx signed a collaboration agreement with TFF Pharmaceuticals to determine the feasibility of formulating RLF-100 as a dry powder using TFF Pharmaceuticals’ thin-film freezing (TFF) technology.

- **“ACTIV-3b/TESICO” trial**: in April 2021, RLF-100 IV was selected for inclusion in the NIH-sponsored global “ACTIV3b/TESICO” phase III trial as one of two drugs including Gilead’s Veklury (remdesivir) in severely ill patients with COVID-19.

- **APR acquisition**: closed in June 2021, adds marketed, niche and near products as well as attractive high margin pipeline projects next to an emerging European sales platform to launch current and future products.
• Supply chain agreements:
  o Bachem Americas: a long-time and cost-effective active pharmaceutical ingredient (API) manufacturer with almost a decade of experience of producing aviptadil, will provide commercial supplies of RLF-100 API with the ability to scale up rapidly.
  o Nephron Pharmaceuticals: will provide the “fill/finish” sterile injectable drug product.
  o Polypeptide: In October 2020, NeuroRx signed an agreement with Polypeptide for the supply of GMP grade Active Pharmaceutical Ingredient (API) of RLF-100 IV providing a second source of procuring API. The Company has agreed to purchase a total of USD 1,010,000 worth of product and services over the contract.
  o Cardinal Health: In August 2021, NRx signed an agreement with Cardinal Health to provide third party logistics and distribution of RLF-100 IV upon EUA approval in the US
  o MannKind: In August 2021, NRx signed an agreement to develop a dry powder inhaler formulation of RLF-100 based on MannKind’s Technosphere platform to extend use to many pulmonary conditions beyond COVID-19
  o AMRI: a global contract and development and manufacturing organization (CDMO) will provide aseptic fill/finish manufacturing of RLF-100 for clinical trial medication at their Glasgow, UK, facility.

• Funding agreements:
  o GEM Global Yield Fund: Funding has been provided by Global Emerging Markets (GEM), Relief’s largest shareholder with currently a ~22% equity stake. Recent financings are sufficient to fund operations and key clinical development projects into late 2023. In January 2021, Relief established a new CHF 50 mn SSF with GEM, with the potential to extend the cash reach substantially beyond this period.
  o Private placements with US institutional investors: In March 2021, gross proceeds of approximately CHF 10 mn was raised in a private placement with a single healthcare-dedicated US institutional investor followed by CHF 15 mn with two US institutional investors in end July 2021.

Relief’s key priorities for the next 12-18 months include:
  • Gain US Emergency Use Authorization (EUA) for RLF-100 IV in COVID-19 induced ARDS around year-end 2022 (initial EUA declined by FDA in December 2020, second EUA declined in November 2021), marking first commercial sales of RLF-100
  • Resolve ongoing dispute with US partner NRx (formerly NeuroRx) and CEO Dr. Javitt either amicably, through a settlement, or the recently filed lawsuit in the Supreme Court of the State of New York. Mediation to resolve litigation to start early January 2022
  • File for EU Conditional Marketing Authorization (CMA) for RLF-100 IV in COVID-19 induced ARDS shortly after a potential US authorization for emergency use (H1 2023)
  • Alternatively, consider starting EU phase IIb/III trial of RLF-100 IV in COVID-19 induced ARDS if positive “COVID-AIV” trial not sufficient for EU CMA
  • Complete US single pivotal phase IIb/III “AVICOVID-2” trial of RLF-100 INHALED in prevention COVID-19 related ARDS with results due H1 2022
  • Integrate APR and Relief organizations and determine and execute key projects and priorities to accelerate growth.
• US approval of ACER-001 in UCDs with a 5 June 2022 PDUFA date and start POC trials in MSUD
• After successfully closing of the AdVita acquisition in July 2021 to expand the scope of development of RLF-100 INHALED in indications such as pulmonary sarcoidosis and checkpoint inhibitor pneumonitis (CIP)
• Consider starting potentially pivotal phase IIb/III trial of RLF-100 IV in non-COVID-19 ARDS with a potential supplemental New Drug Application (sNDA) pathway applied.
• Start phase IIb dose ranging trial of RLF-100 INHALED in pulmonary sarcoidosis in 2022 with results due 2023
• Accelerate clinical development plan for APR TD-011 in epidermolysis bullosa (EB).
• Strategically grow management team as the clinical pipeline evolves
• Explore partnerships and distribution agreements for RLF-100 in regions where Relief does not intend to establish its own commercial infrastructure (e.g., emerging markets)
• Continue to expand the clinical pipeline through selective product in-licensing and/or M&A

Almost CHF 120 mn raised since 2016
In 2020, Relief has been very successful in fund raising, when more than 90% of funds since inception were raised on the back of encouraging early data of RLF-100 in treating critically ill COVID-19 patients with respiratory complications in the ongoing US open label Expanded Access Program. Since the company went public via a reverse merger in 2016, the company has raised a total of CHF 116.3 mn, mainly from GEM Global Yield Fund, LLC, which has become Relief’s largest shareholder with currently a ~22% equity stake in Relief.

Recent financings have raised approximately CHF 57.9 mn, largely through the Share Subscription Facility (SSF) agreement with GEM, which was concluded in September 2020. In January 2021, Relief established a new CHF 50 mn SSF with GEM, which it intends to use, if necessary, to fund the purchase of additional commercial supply of RLF-100 to meet demand as needed, to fund the potential definitive agreement with Acer on the development and commercialization of ACER-001 in UCDs and MSUD, as well as pursue further business development opportunities. Relief has the right to periodically, during a timeframe of up to three years, issue and sell shares to GEM. Relief will control the timing and maximum amount of any draw down, and retains the right, not the obligation, to draw down on the full commitment amount. GEM undertakes to subscribe to or acquire ordinary registered Relief common shares. Future subscription prices under the SSF will correspond to 90% of the average of the closing bid prices on the SIX Swiss Exchange during the reference period, which corresponds to 15 trading days following Relief’s draw down notice. In March 2021, Relief raised gross proceeds of approximately CHF 10 mn in a private placement to a single healthcare-dedicated US institutional investor. An additional CHF 15 mn gross proceeds were raised in a private placement to two US institutional investors in July 2021. Since August 2021, Relief has raised approximately CHF 26 mn from treasury shares, which constitutes a meaningful recent source of equity funding.
Life Cycle Positioning – Speculative

We qualify Relief’s risk profile as Speculative with currently no substantial product revenues with a current cash runway into late 2023. The CHF 50 mn SSF with GEM has the potential to increase Relief’s cash reach substantially beyond this period, albeit at the cost of share dilution. 2023 should be a transformational year for Relief, upon a potential grant of an US EUA for RLF-100 IV in COVID-19 induced ARDS expected around year-end 2022, marking first commercial sales for RLF-100. Other countries and regions outside the US such as the EU may also approve RLF-100 IV for COVID-19 induced ARDS due to the current lack of effective and safe treatments. This should lead to a substantial increase in Relief’s value as well as a marked improvement in the company’s risk profile (see Important Disclosures for our Risk Qualification).
Risk-adjusted sum-of-parts NPV points to a fair value of CHF 0.520 per share
We derive a sum-of-parts risk-adjusted (r)NPV of CHF 0.520 per share for Relief, with estimated cash and cash equivalents of CHF 0.010 per share (11 November 2021) and overhead expenses of CHF 0.033 per share, assuming a WACC of 7% (reflecting the low Swiss interest environment).

### Relief’s key drivers, include:

**RLF-100 IV in COVID-19 induced ARDS - rNPV of CHF 0.030/share**
In November 2021, the FDA declined to grant US Emergency Use Authorization (EUA) for RLF-100 IV based on the positive 60-Day topline trial results of the phase IIb/III “COVID-AIV” trial of RLF-100 IV in 196 patients with COVID-19 induced ARDS citing insufficient data to establish a positive benefit/risk. We believe this pushes back a potential new EUA filing by roughly a year upon positive ACTIC-3b/TESICO trial results expected in Q4 2022. A US EUA could trigger a potential Conditional Marketing Authorization (CMA) in the EU in 2022. We now forecast peak sales of CHF 200 mn to be reached in 2023 and thereafter sales to gradually decrease due to the expected decline in COVID-19 cases thanks to the rollout of broad-scale COVID-19 vaccination programs globally. Outside the US/EU, we assume pandemic stockpiling sales for RLF-100 IV. We calculate a rNPV of CHF 0.030/share for RLF-100 in COVID-19 induced ARDS, considering the profit split agreement with NRx in the US (50/50 profit split), Europe (85/15 profit split in favor of Relief) and ROW (80/20 profit split in favor of Relief) with a 65% (phase III) success rate and a WACC of 7%.

**RLF-100 INHALED in prevention COVID-19 related ARDS – rNPV of CHF 0.132/share**
The prevention of respiratory failure in patients with COVID-19 moderate and severe disease represents a larger market opportunity than for COVID-19 induced ARDS as far more patients are affected (~4x more patients than COVID-19 induced ARDS patients) with a longer treatment duration (4 weeks treatment compared to ~1 week) resulting in a higher price per treatment course per patient. We forecast peak sales of CHF 500+ mn for RLF-100 INHALED in prevention COVID-19 related ARDS. Our forecasts are based on the same decline in global COVID-19 cases as we expect for COVID-19 induced ARDS. The US phase IIb/III “AVICOVID-2” trial started in February 2021 with topline results due in H1 2022 with a US launch in H2 2022 followed by the EU in 2023. We calculate a rNPV of CHF 0.132 per share for RLF-100 INHALED in prevention COVID-19 related ARDS considering the global NRx profit split agreement with a 65% (phase II/III) success rate.
RLF-100 IV in non-COVID-19 related ARDS – rNPV of CHF 0.075/share
We forecast peak sales for RLF-100 in ARDS not caused by COVID-19 but from other causes such as sepsis, pancreatitis, trauma or pneumonia, to amount to CHF ~500 mn. Phase IIb/III trials are expected to start in 2022 with results due early 2023. Assuming a supplemental New Drug Application (sNDA) approval, US launch could occur in 2023. EU launch is expected in 2024. For RLF-100 IV in ARDS (non-COVID-19), we calculate a rNPV of CHF 0.075 per share assuming a 35% (POC established) success rate and considering the global NRx profit split agreement.

RLF-100 INHALED in pulmonary sarcoidosis – rNPV of CHF 0.049/share
We forecast peak sales of RLF-100 INHALED in pulmonary sarcoidosis to amount to CHF 500+ mn with first launches expected in 2025. A phase IIb dose ranging trial is expected to start in 2022. Pulmonary sarcoidosis is a rare disease caused by inflammation, particularly in the lungs with limited treatment options. Pulmonary sarcoidosis was the initial indication Relief targeted for clinical development of RLF-100 before the COVID-19 pandemic emerged in early 2020 and COVID-19 indications were prioritized. We calculate a rNPV of CHF 0.049 per share for RLF-100 INHALED in pulmonary sarcoidosis assuming a 35% (POC established) success rate and considering the global NRx profit split agreement.

ACER-001 in urea cycle disorders (UCDs) – rNPV of CHF 0.043/share
We forecast peak sales of ACER-001 in urea cycle disorders (UCDs) to amount to CHF 130+ mn. ACER-001, in-licensed from Acer Therapeutics, is a novel powder and immediate release (IR) formulation of sodium phenylbutyrate, is targeted to provide a compelling alternative to Horizon Therapeutics’ Buphenyl (glycerol phenylbutyrate) with a novel taste-masking formulation that potentially can be taken without food at a competitive pricing. The FDA set a 5 June 2022 PDUFA data when it expects to conclude its review of ACER-001 in UCDs with a first launch in the US to occur in 2022. Relief is entitled to 60% of net profits in the Acer territories (US, Canada, Brazil, Turkey and Japan), while Acer will receive a 15% net royalty on ROW sales by Relief, next to regulatory milestones upon approval in the EU. We calculate a rNPV of CHF 0.043 per share for ACER-001 in UCD assuming an 80% (Section 505(b)(2)) success rate.

ACER-001 in Maple Syrup Urine Disease (MSUD) – rNPV of CHF 0.015/share
We forecast peak sales of ACER-001 in Maple Syrup Urine Disease (MSUD) to amount to CHF 80+ mn. Based on encouraging POC trial results, Acer and Relief plan to start phase IIb/III development of ACER-001 in MSUD in 2022 with a potential launch in the US in 2023 and in the EU in 2024. We calculate a rNPV of CHF 0.015 per share for ACER-001 in MSUD assuming a 35% (POC) success rate and considering the regulatory milestones, profit split, and sales royalties according to the proposed global agreement with Acer.

Golike in phenylketonuria (PKU) – rNPV of CHF 0.028/share
We forecast peak sales of CHF 50+ mn for the Golike, the first food for special medical purposes (FMSP) engineered product for patients with phenylketonuria (PKU) with a drug delivery technology offering better metabolic management and better compliance due to minimized taste, odor, and aftertaste. Golike is a family of products covering main age groups and individual habits including sachets, shake & drinks and bars being rolled out in the EU by distribution partners. Relief expects to launch Golike in the US in H1 2022. US approval as a prescription-only treatment could boost peak sales to CHF 200+ mn. Our NPV for Golike amounts to CHF 0.028 per share.
APR-TD011 in epidermolysis bullosa (EB) – rNPV of CHF 0.170 per share
Epidermolysis bullosa (EB) is a group of rare, genetic, life-threatening connective tissue disorders characterized by skin blistering throughout the body and risk of severe impact to external organs affecting ~250,000 patients worldwide. APR-TD011 is HClO sprayable solution that combines strong antimicrobial action and anti-inflammatory properties with the potential to become one of the first products ever to be approved for EB. A preliminary POC trial showed improvement in skin blistering and tissue repair in just two weeks. The US FDA granted Orphan Drug Dedication for APR-TD011 in 2019 providing 7-years marketing exclusivity from approval in the US. Discussions with regulatory authorities are ongoing to finalize clinical development path with a potential launch in 2026. We forecast peak sales for APR-TD011 to amount to CHF 900+ mn in EB and calculate a rNPV of CHF 0.170 per share assuming a 35% (POC established in wound healing) success rate.

Currently no value attributed to early-stage pipeline projects
We have conservatively not accounted for Relief's early-stage pipeline projects due to the lack of sufficient proof-of-concept now. Relief's unadjusted NPV provides a "sneak preview" on what the value could amount to, if all our assumptions were reached.

RLF-100 INHALED in CIP – phase I, launch 2025
The increasing use of immune checkpoint inhibitor (ICI) therapy in cancer has brought new hope of survival to patients with advanced tumors. However, the immune system activated by ICI therapy, mainly activated T-cells, can attack normal tissues and organs in the body and lead to a variety of adverse effects. In the lung, these attacks can induce checkpoint inhibitor pneumonitis (CIP) and is one of the complications associated with ICI therapy. CIP is defined as the occurrence of dyspnea and/or other respiratory symptoms, together with new inflammatory lesions on chest computed tomography (CT) after ICI treatment, following exclusion of pulmonary infection, tumor progression, and other reasons. The incidence of CIP reported in clinical trials was between 3% to 5%. The risk factors for CIP are unknown. Corticosteroids are currently the basic treatment for CIP, however, have side effects, which have to be closely monitored, while a number of patients are insensitive to corticosteroid treatment. There are no optimal recommendations for treatment of refractory CIP to date. Based on a compelling case report where a patient with refractory CIP was given RLF-100 INHALED over a period of six months resulting in improved lung function and good clinical conditions, Relief plans to develop the compound in this indication and to start a POC trial followed a phase IIb/III trial in CIP. First launches could occur in 2025 with peak sales conservatively amounting to CHF 150+ mn. Due to the lack of sufficient POC, we exclude forecasts for RLF-100 INHALED in CIP, yet

APR niche disorders and early-stage pipeline projects
Relief is currently assessing which APR products offer the optimal strategic fit combined with differentiation that can offer strong growth potential. Niche disorders include, Nexodyn AOS, a sprayable HClO solution for acute and chronic wounds; Setofilm/Zuplenz/Ondisolve, an oral dispersible film containing ondansetron for treating chemotherapy-, radiotherapy- and postoperative nausea and vomiting; Sentinox a ready to market sprayable HClO solution to block transmission of SARS-Cov-2 virus and APR-TM011 approved as a Class III medical device in the EU for the prevention and treatment of skin rashes associated with cancer treatments.
Sensitivities that can influence our valuation

**Funding risk:** With a cash position of CHF 45 mn, Relief has a cash runway into late 2023 without factoring in potential revenues from RLF-100 sales, which could start as early as 2022, or exploiting the CHF 50 mn SSF with GEM. The company is fully financed to successfully complete RLF-100’s COVID-19 trials in the US and EU and to fund ACER-001 development in UCDs and MSUD.

**Development risk:** RLF-100 targeted indications are in different phases of clinical development. Most advanced are COVID-19 induced ARDS and prevention COVID-19 related ARDS, both in pivotal development with a 65% (phase II/III) success rate, followed by non-COVID-19 related ARDS and pulmonary sarcoidosis with a 35% (POC established) success rate. All indications for RLF-100 are targeted for respiratory disease, which could present a cluster risk. The pending dispute and US lawsuit with NRx and CEO Dr. Javitt could potentially delay clinical development timelines. Mediation is expected to start early January 2022. ACER-001 in UCDs is developed under Section 505(b)(2) providing an alternative pathway for filing an NDA with an 80% success rate and a 35% (POC) success rate in MSUD. For APR we only include APR-TD011 in EB with a 35% (POC) success rate.

**Commercialization risk:** Both RLF-100 and ACER-001 are specialty drugs, which do not require large sales forces. The sales uptake of RLF-100 in the two COVID-19 indications is largely dependent on the number of COVID-19 infections, hospitalizations and stockpiling, with yet unknown impact by global vaccination programs on significantly reducing the number of infections. Potential new market entrants for treating COVID-19 patients may also impact sales uptake. The emerging APR European specialist sales force can be leveraged and expanded for upcoming product launches.

**Pricing and reimbursement risk:** Pricing and reimbursement for both RLF-100’s COVID-19 indications should not provide a large hurdle given the lack of effective treatments and the ongoing global pandemic. We believe our pricing assumptions may prove conservative with the “COVID-AIV” topline results showing a significant survival benefit. ACER-001 is expected to be competitively priced vs. existing drugs for UCDs. Treatment costs for APR-TD011 in EB represents pricing for an orphan drug indication with no effective treatments.

**Manufacturing risk:** Relief has secured sufficient RLF-100 treatment courses for its first approved indications with Bachem Americas, Nephron and AMRI. Multiple future distribution partnerships are currently under discussion.

**Intellectual property risk:** RLF-100 could enjoy US patent protection until 2029 with 5-year Hatch Waxman patent extension reaching to 2034 and 5 years NCE exclusivity. The EU patent of RLF-100 expires in July 2026. Market exclusivity in the EU beyond 2026 depends on whether RLF-100 is successful in receiving orphan drug exclusivity for COVID-19 induced ARDS. Assuming an earlier approval of RLF-100 INHALED in prevention COVID-19 related ARDS, cheaper generic versions of RLF-100 INHALED could appear after 2026 in the EU hampering sales uptake of RLF-100 INHALED in pulmonary sarcoidosis even when it enjoys orphan drug exclusivity for sarcoidosis. We conservatively assume cheaper generic competition in the EU after 2026. ACER-001 is likely to enjoy 7 years (US) and 10 years (EU) orphan drug exclusivity in both UCDs and MSUD as well as APR-TD011 in EB. A recently issued US formulation patent extends ACER-001 protection into 2036.
<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Event Date</th>
<th>Description</th>
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| | | **Catalysts**

## 2021

### 17 Nov 2021
- **PREVENTION COVID-19 RELATIVE INVESTMENT**
- **INDICATORS**

### 29 Nov 2021
- **AVICOVID-1**
- **TOPLINE DATA**
- **FDA REVIEW**

### 30 Nov 2021
- **AVICOVID-2**
- **TOPLINE DATA**

### 1 Dec 2021
- **PERTURBATION**
- **MAA FILING**

### 2 Dec 2021
- **SURVIVAL**
- **NDA**

### 4 Dec 2021
- **ACER-005**
- **UNRESTRICTED**
- **PRIVATE PLACEMENT**

### 7 Dec 2021
- **ACER-001**
- **RELIEF CORP**
- **PRIVATE PLACEMENT**

### 12 Dec 2021
- **ACER-001**
- **RELIEF CORP**

### 15 Dec 2021
- **ACER-001**
- **RELIEF CORP**

### 17 Dec 2021
- **ACER-001**
- **RELIEF CORP**

### 20 Dec 2021
- **ACER-001**
- **RELIEF CORP**

### 21 Dec 2021
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- **RELIEF CORP**

### 22 Dec 2021
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- **RELIEF CORP**

### 24 Dec 2021
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- **RELIEF CORP**

### 28 Dec 2021
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- **RELIEF CORP**

### 29 Dec 2021
- **ACER-001**
- **RELIEF CORP**

### 30 Dec 2021
- **ACER-001**
- **RELIEF CORP**

### 31 Dec 2021
- **ACER-001**
- **RELIEF CORP**

Please see important research disclosures at the end of this document.
Technology & Pipeline

TECHNOLOGY PLATFORM - No proprietary technology platform but a S&D approach

Relief does not have a proprietary technology platform. The company applies a “search and development” approach to build its pipeline with compounds to “provide patients with therapeutic RELIEF from serious diseases with high unmet medical need” with a special focus on respiratory disease and orphan drug indications. Relief plans to expand its clinical pipeline through selective product in-licensing and/or M&A deals.

PIPELINE - Targeting multiple respiratory disorders and rare diseases

### PRODUCT PIPELINE

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>DRUG CLASS</th>
<th>INDICATION</th>
<th>STATUS</th>
<th>LAUNCH YEAR</th>
<th>PARTNER</th>
<th>PEAK SALES</th>
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<td>RLF-100 INHALED</td>
<td>INHALED SYNTHETIC HUMAN VASOACTIVE INTESTINAL PEPTIDE (VIP)</td>
<td>COVID-19 INDUCED ARDS**</td>
<td>PHASE III</td>
<td>2023</td>
<td>NIX (US, CANADA, ISRAEL)</td>
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<td>PULMONARY SARCOIDOSIS</td>
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<td>TASTE-MASKED, IMMEDIATE-RELEASE FORM OF SODIUM PHENYL BUTYRATE</td>
<td>UREA CYCLE DISORDERS (UCD)</td>
<td>PHASE III</td>
<td>2022</td>
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<td>ACER-001</td>
<td>TASTE-MASKED, IMMEDIATE-RELEASE FORM OF SODIUM PHENYL BUTYRATE</td>
<td>MAPLE SYRUP URINE DISEASE (MSUD)</td>
<td>PHASE I</td>
<td>2024</td>
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<td>APR-TD011</td>
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* ** = INTRAVENOUS (IV) INFUSION, ** = INHALED SYNTHETIC HUMAN VASOACTIVE INTESTINAL PEPTIDE (VIP) PLANNED DOSE RESPONSE, *** = EMERGENCY USE AUTHORIZATION ESTIMATES AS OF 22 NOVEMBER 2021

### After divesting atexakin alfa, a low-dose formulation of interleukin-6 (IL-6) in development for treating neuropathy, to Sonnet BioTherapeutics (NASDAQ symbol: SONN) in August 2019, Relief’s key pipeline project is aviptadil (designated RLF-100™ and branded under the trade name ZYESAMI™ in the US). To strengthen and expand its pipeline, Relief signed a collaboration and license agreement with Acer Therapeutics (symbol: ACER), based in Newton, Massachusetts, USA, in March 2021, for the worldwide development and commercialization of ACER-001 a novel powder formulation of sodium phenylbutyrate (NaPB) designed to be taste-masked and immediate release (IR). ACER-001 adds a second late-stage pipeline project to Relief with a relatively high 80% (Section 505(b)(2)) success rate in urea cycle disorders (UCDs) and 35% (POC) success rate in maple syrup urine disease (MSUD), targeting lucrative, high priced, high margin, rare disease market opportunities.

In June 2021, Relief acquired the privately held Applied Pharma Research (APR), based in Balerna, Switzerland with sales and marketing subsidiaries in Rome, Italy, and Offenbach, Germany, which transformed Relief in a fully integrated commercial-stage biopharmaceutical company from a development-stage company. The APR acquisition brings to Relief a pipeline of product candidates at various stages of development, including marketed products, near-to-market products, and a varied clinical development portfolio that offers exciting growth opportunities, with multiple synergies across Relief’s pipeline projects.
Relief’s key pipeline projects, include:

I) RLF-100 rapidly repurposed for COVID-19 respiratory complications
RLF-100 is a patented formulation of vasoactive intestinal polypeptide (VIP). VIP in combination with phentolamine mesylate, branded Invicorp by Senetek Pharmaceuticals, was originally developed as an intracavernosal injection for the treatment of erectile dysfunction and was approved in 1998 and is marketed in Europe. RLF-100 became part of Relief’s pipeline through Relief’s reverse merger with the corporate successor of mondoBIOTECH, originator of the drug, with the plan to reposition the compound in respiratory disease starting with pulmonary sarcoidosis. The rapid onset of the SARS-CoV-2 virus (COVID-19) pandemic in early 2020 resulted in a rapid repositioning of RLF-100 in treating and preventing critical COVID-19 patients with respiratory failure with the highest priority. Although most COVID-19 cases are mild, older patients and those with comorbidities are at increased risk of developing a cytokine storm, characterized by a systemic inflammatory response leading to acute respiratory distress syndrome (ARDS) and organ failure. Acute respiratory failure is the primary cause of death in critically ill COVID-19-infected patients, with up to 80% of these patients dying despite intensive care and mechanical ventilation.

VIP involved in the control of airway tone, mucus secretion and vascular relaxation
RLF-100 is a recombinant form of vasoactive intestinal polypeptide (VIP), an abundant biologically active endogenous human peptide that was discovered in 1970 and possesses antiproliferative, anti-inflammatory, anti-cytokine, and immune-regulatory activities in animal models of respiratory distress, acute lung injury, and inflammation as has been shown in more than 100 peer-reviewed studies. Although first identified in the intestinal tract, VIP is now known to be produced throughout the body and to be primarily concentrated in the lungs where its predominant biological activity is observed. VIP is a member of the secretin family of peptides. It is one of the most important non-adrenergic, non-cholinergic inhibitory transmitters in the lung, where it is involved in the control of airway tone, vascular relaxation and airway mucus secretion.

In the respiratory system of humans, VIP-containing nerve fibers have been described in tracheo-bronchial smooth muscle, around submucosal glands and in the walls of pulmonary and bronchial vessels. The biological functions of VIP are mediated through two receptors, the vasoactive intestinal peptide receptor type 1 (VPAC1 receptor) and type 2 (VPAC2 receptor) and belong to the G protein-coupled receptor family. Both VPAC1 and VPAC2 receptors are expressed in human airways: VPAC1 receptor by bronchial epithelial cells, bronchial and vascular smooth muscle, and VPAC2 receptor by bronchial epithelial cells and bronchial glands.

RLF-100 has been tested alone in several pilot and phase II trials for respiratory indications, including:

- **Acute lung injury (ALI):** 8 patients were given a single infusion of 50 picomol/hour/kg of body weight of RLF-100 IV for 6 or 12 hours
- **Pulmonary sarcoidosis:** 20 patients were given 50 microgram (µg) RLF-100 INHALED by nebulizer 4 times daily for 4 weeks
- **Pulmonary hypertension:** 48 patients were given escalating doses from 50 – 200 µg RLF-100 INHALED by nebulizer 4 times daily for 12 weeks
- **Pulmonary fibrosis:** 15 patients were given 100 µg RLF-100 INHALED by nebulizer 3 times daily for 24 weeks
In the pulmonary sarcoidosis and acute lung injury trials, a significant reduction of inflammation was observed with a decrease in TNF-alpha levels. In all trials, RLF-100 was well tolerated with very few side effects. The most notable of these were diarrhea and transient 10 mmHg hypotension at high intravenous doses. There is no lethal dose of VIP with extensive safety documentation in four animal species, including primates.

**RLF-100 prevents deadly cytokine storm and viral replication of COVID-19**

ARDS is the primary cause of death in COVID-19. RLF-100’s active ingredient, vasoactive intestinal polypeptide (VIP), has demonstrated an immediate clinical response in patients with COVID-19 induced ARDS. The cause of death in COVID-19 is broadly attributed to cytokine storm – i.e., a massive release of inflammatory cytokines as viral particles infect and then cause rupture of pulmonary epithelium cells – that is not readily manageable using commercially available anti-cytokine drugs. Cytokine inhibition alone has been shown to be insufficient because the lethal damage caused by the coronavirus stems from viral replication in the Alveolar Type II (ATII) cell, with resulting cytopathic effects and cell rupture.

COVID-19 induced ARDS is caused by selective infection of the ATII cell by the SARS-CoV-2 coronavirus. The ATII cells are particularly vulnerable because of their high surface density of Angiotensin Converting Enzyme type 2 (ACE2) cell surface receptors, which serve as the route of entry for the virus. These specialized cells manufacture surfactant that coats the lung and is essential for oxygen exchange. Loss of surfactant causes collapse of the air sacs (alveolae) in the lung and results in respiratory failure.

The SARS-CoV-2 virus enters the ATII cell through binding of its spike protein to ACE2 surface receptors. ACE2 is not present on Alveolar Type I (ATI) cells, which comprise 95% of the pulmonary epithelium and those cells are not infected by the corona virus. Most importantly, approximately 70% of the VIP binds uniquely to VPAC1 receptors on ATII cells in the lung that is critical to transmission of oxygen to the body, the same cells that bind the SARS-CoV-2 virus via their ACE2 receptors. VIP protects those cells and the surrounding pulmonary epithelium by inhibiting replication of the SARS-CoV-2 virus, blocking cytokine synthesis, preventing apoptosis, and upregulating the production of surfactant, which is critical to pulmonary oxygenation.

While VIP clearly prevents cytokine storm, its primary effect is to block viral replication in the first place and to upregulate the production of surfactant that is critical to blood oxygenation. **Hence, VIP represents the first COVID-19 therapeutic to directly combat the replication of the SARS-CoV-2 virus at the site of injury.** Other than RLF-100, no currently proposed treatments for COVID-19 specifically target these vulnerable Type II cells. The US FDA has granted Investigational New Drug (IND) licenses for multiple pivotal clinical trials of RLF-100 in COVID-19 respiratory failure.

**RLF-100 has potential in treating and preventing respiratory failure, including:**

- **COVID-19 induced ARDS:** treating critically ill COVID-19 patients hospitalized on mechanical ventilation with a poor prognosis (positive 60-day topline results US phase IIb/III “COVID-AIV” trial reported in March 2021, US EUA declined on 4 November 2021, next pivotal “ACTIV-3b/TESICO” trial to report topline results in Q4 2022)
- **Prevention COVID-19 related ARDS:** preventing COVID-19 patients at risk of developing critical respiratory failure or life-threatening ARDS (US phase IIb/III “AVICOVID-2” trial started in February 2021 with results due in H1 2022)
• Non-COVID-19 related ARDS: treating patients with ARDS from other causes than COVID-19 with a high unmet medical need due to the lack of effective treatments. Relief considers starting a pivotal phase IIb/III trial with a potential supplemental New Drug Application (sNDA) pathway applied.

• Pulmonary sarcoidosis: A small POC trial showed promise in pulmonary sarcoidosis. Relief plans to start a phase IIb dose ranging trial of RLF-100 INHALED in patients with pulmonary sarcoidosis in 2022. The company expects first launches in 2025.

• Checkpoint inhibitor pneumonitis (CIP): is a potentially fatal complication if not treated correctly in 3-5% of patients receiving checkpoint inhibitors. Relief and AdVita are considering development of RLF-100 INHALED in CIP.

II) ACER-001 a novel taste-masked IR formulation of NaPB for various inborn errors of metabolism

ACER-001 is a taste-masked, immediate-release (IR) proprietary formulation of sodium phenylbutyrate (NaPB) developed by Acer using a microencapsulation process. ACER-001 microparticles consist of a core center, a layer of active drug, and a taste-masking coating which dissolves in the stomach, allowing taste to be neutralized while still allowing for rapid systemic release. ACER-001 is being developed for the treatment of various inborn errors of metabolism, including UCDs and MSUD. Acer has been granted Orphan Drug Designation (ODD) by the FDA for the MSUD indication.

• Urea cycle disorders – UCDs: ACER-001 is targeted to provide a compelling alternative to Horizon Therapeutics’ Buphenyl (glycerol phenylbutyrate) with a novel taste-masking formulation that potentially can be taken without food at a competitive pricing. The FDA set a 5 June 2022 PDUFA date with the US launch to occur first in 2022.

• Maple syrup urine disorder – MSUD: Based on encouraging POC trial results, Acer and Relief plan to start phase IIb/III development of ACER-001 in MSUD in 2022 with a potential launch in the US and EU in 2024.

III) Selected APR pipeline projects – Golike and APR-TD011 in rare diseases

The acquisition of APR expands Relief’s pipeline further with compounds targeting inherited metabolic recessive disorders and niche disorders. APR has developed these compounds with the help of its two core formulation technologies including its Physiomimic™ Technology that is able to modify the release of clinically relevant amino acids by prolonging their absorption profiles and Tehclo™ a globally patented nano-technology platform applied to the production of a unique hypochlorous acid (HClO) solution that ensures the most consistent quality for best-in-class clinical outcomes.

• Golike (phenylketonuria – PKU): Golike is the first line of food for special medical purposes (FSMP) engineered with APR’s drug delivery Physiomimic™ Technology offering an improved metabolic management for patients with PKU and a better compliance thanks to minimized taste, odor and aftertaste. Golike is approved in the EU and currently rolled out by distribution partners. US launch is expected by H1 2022.

• APR-TD011 (epidermolysis bullosa – EB): is a sprayable hypochlorous (HClO) sprayable solution stemming from APR’s Tehclo™ that combines strong antimicrobial activity with anti-inflammatory properties with the potential to become one of the first products ever approved for EB. A preliminary proof of concept trial showed promising results with improvement of skin blistering and tissue repair in just two weeks treatment. Relief expects to start phase II development in mid 2022 once the clinical development program has been finalized with regulators and expects first launches in 2026.
In the following section we will provide an in-depth analysis and forecasts for Relief’s key drivers:

1. RLF-100 IV in COVID-19 induced ARDS  
2. RLF-100 INHALED in prevention COVID-19 related ARDS  
3. RLF-100 IV in non-COVID-19 ARDS  
4. RLF-100 INHALED in pulmonary sarcoidosis  
5. ACER-001 in UCDs  
6. ACER-001 in MSUD  
7. Golike in PKU  
8. APR-TD011 in EB
Forecasts & Sensitivity Analysis

RLF-100 (COVID-19 induced ARDS & prevention COVID-19 related ARDS; non-COVID-19 related ARDS)

Product Analysis

I) RLF-100 IV in COVID-19 induced ARDS:
Peak sales CHF 200+ mn; rNPV CHF 0.030/share
We forecast global peak sales of CHF 200 mn for RLF-100 IV in patients with COVID-19 induced ARDS. US Emergency Use Authorization (EUA) based on the pivotal “COVID-AIV” trial was declined in November 2021. A new EUA filing could occur roughly a year later upon positive phase IIII “ACTIV-3b/TESICO” trial results expected in Q4 2022. A US EUA grant around year-end 2022, could potentially trigger EU conditional marketing authorization (CMA), marking first commercial launches for RLF-100, which would be transformational for Relief. Outside the US/EU, we assume pandemic stockpiling sales for RLF-100 IV. We assume patent protection until 2034 (US) and 2026 (EU). We calculate a rNPV of CHF 134 mn or CHF 0.030/share with a 65% (phase III) success rate (for details see page 40).

II) RLF-100 INHALED in prevention COVID-19 related ARDS:
Peak sales CHF 500+ mn; rNPV CHF 0.132/share
For RLF-100 INHALED in prevention COVID-19 related ARDS, we forecast global peak sales to reach CHF 500+ mn assuming US and EU approval and launch in 2022. The sales potential for prevention COVID-19 related ARDS is higher than COVID-19 induced ARDS due to more COVID-19 patients affected and a longer treatment duration. We calculate a rNPV of CHF 583 mn or CHF 0.132/share assuming a 65% (phase II/III) success rate (for details see page 44).

III) RLF-100 IV in non-COVID-19 related ARDS:
Peak sales CHF 450+ mn; rNPV CHF 0.075/share
Global peak sales for RLF-100 IV in ARDS not caused by COVID-19 are expected to amount to roughly CHF 450+ mn assuming US launch in 2023 and EU launch in 2024. We calculate a rNPV of CHF 330 mn or CHF 0.075/share assuming a 35% (POC established) success factor (for details see page 47).

Significant market opportunity in COVID-19 disease and beyond
Early proof-of-concept (POC) data generated with aviptadil (designated RLF-100™ and branded under the trade name ZYESAMI™ in the US) in acute respiratory distress (ARDS) triggered the decision to assess the potential of RLF-100 in treating and preventing rapid respiratory decline in critically ill COVID-19 patients, which leads to life-threatening ARDS. Up to 80% of these patients die when critically ill, despite intensive care and mechanical ventilation. ARDS is the hallmark complication in critically ill COVID-19 patients, with no effective and safe treatments available, yet. Early promising results from the ongoing US open label Expanded Access Program (EAP) dubbed “SAMICARE” showed a 72% survival rate for critically ill COVID-19 patients with ARDS and on mechanical ventilation treated with RLF-100 IV. Last year, in a remarkable flurry of agreements, Relief secured a strategic...
development and commercialization partnership for RLF-100 with the US-based firm NRx, sufficient funding for the clinical development of RLF-100 in its key respiratory indications through major shareholder GEM Global Yield Fund, and established supply chain agreements with Bachem Americas and Nephron Pharmaceuticals and ordered sufficient drug substance to treat large number of COVID-19 patients with RLF-100.

RLF-100 has potential in treating and preventing respiratory failure, including:

I) COVID-19 induced ARDS: treating critically ill COVID-19 patients hospitalized on mechanical ventilation with a poor prognosis (positive 60-day topline results US phase IIb/III “COVID-AIV” trial reported in March 2021, US EUA declined November 2021, “ACTIV-3b/TESICO” phase III topline results due Q4 2022)

II) Prevention COVID-19 related ARDS: preventing COVID-19 patients at risk of developing critical respiratory failure or life-threatening ARDS (US phase IIb/III “AVICOVID-2” trial started in February 2021 with results due in H1 2022)

III) Non-COVID-19 related ARDS: treating patients with ARDS from other causes than COVID-19 with a high unmet medical need due to the lack of effective treatments (phase IIb/III trial may start 2022 with results due in 2023)

The two COVID-19 indications gained highest priority due to the pandemic

The first two indications for RLF-100 have the highest priority given the high number of critically ill COVID-19 patients who develop life-threatening ARDS, overwhelming hospitals and intensive care units (ICUs) in many countries, globally. As a result, many countries have implemented strict lockdown measures at a high economic and social cost. The focal point of these lockdown measures is to prevent hospitals and ICUs to be overwhelmed with critically ill COVID-19 patients and being forced to ration lifesaving equipment and interventions to these patients as well as other critically ill patients. It is believed the SARS-CoV-2 pandemic is likely become an endemic virus. In the endemic phase, the number of infections becomes relatively constant across years, allowing for occasional flare-ups. To reach this steady state could take a few years or decades, depending on how quickly populations develop immunity. In particular, the continual emergence of new coronavirus variants that may be immune or more resistant to current vaccines pose a risk. Subsequently, the need for new safe and effective treatments for COVID-19 patients is expected to persist for many years to come.

Positive topline results US “COVID-AIV” trial with NRx applying for US EUA

In June 2020, Relief’s US partner NRx started the single potentially pivotal US phase IIb/III “COVID-AIV” trial of RLF-100 IV in 196 patients with Covid-19 induced ARDS based on the promising early results seen in the US open label EAP “SAMICARE”. In March 2021, NRx reported positive topline results after 60 days treatment. Across all patients and sites, RLF-100 IV met the primary endpoint for successful recovery from respiratory failure at days 28 (p=0.014) and 60 (p=0.013) and also demonstrated a meaningful benefit in survival (p<0.001) after controlling for ventilation status and treatment site. Based on these positive results NRx applied to the FDA for Emergency Use Authorization (EUA) on 31 May 2021. On 4 November 2021, the FDA declined EUA citing insufficient data to establish a positive benefit/risk. This pushes back a potential new EUA filing by roughly a year upon positive phase III “ACTIV-3b/TESICO” topline results expected in Q4 2022. If authorized for emergency use, first commercial sales could follow shortly after approval. Upon a US EUA grant, Relief expects to apply for EU Conditional Marketing Authorization (CMA) for RLF-100 IV in COVID-19 induced ARDS adding to the commercial potential. Relief may not have
to conduct a similar phase IIb/III trial in the EU if European regulators agree to accept the US pivotal trial results as indicative of RLF-100 IV’s safety and efficacy. We forecast peak sales in COVID-19 induced ARDS could amount to CHF 200 mn.

In February 2021, NRx started the US phase IIb/III “AVICOVID-2” trial in the prevention of COVID-19 related ARDS to assess the impact of RLF-100 INHALED on preventing respiratory failure in moderate to severe COVID-19 patients with respiratory symptoms. Results are due in H1 2022. We forecast peak sales of more than CHF 500+ mn, more than double COVID-19 induced ARDS due to the higher number of patients with a longer treatment duration.

In total, RLF-100 could achieve more than CHF 700 mn peak sales in COVID-19 associated respiratory disease, alone. Additionally, Relief expects to develop RLF-100 IV in non-COVID-19 related ARDS, caused by for instance by sepsis, trauma, or other serious lung infections. This would add another CHF 500 mn peak sales to our forecasts.

I) RLF-100 IV in COVID-19 induced ARDS - Peak sales CHF 200 mn; rNPV CHF 0.030/share

Strategic collaboration with NRx to develop and commercialize RLF-100

In March 2020, Relief entered into a clinical development collaboration with the US privately held biopharmaceutical company NeuroRx (now NASDAQ-listed NRx Pharmaceuticals with symbol NRXP). NRx is led by former senior executives of Johnson & Johnson, Eli Lilly, Pfizer and AstraZeneca, including CEO Dr. Jonathan Javitt, who is leading the clinical trials of RLF-100 in COVID-19 related respiratory disease, including the completed US phase IIb/III “COVID-AIV” trial of RLF-100 IV in COVID-19 induced ARDS, which reported positive topline results in March 2021, and the ongoing US phase IIb/III “AVICOVID-2” trial of RLF-100 INHALED in prevention of COVID-19 related ARDS that started in February 2021 with results expected in H1 2022.

NRx Collaboration Agreement – ongoing dispute & lawsuit leading to delays

In September 2020, the relationship with NRx was formalized with an exclusive global collaboration agreement on RLF-100 to accelerate development and commercialization in key markets. Both companies agreed to share all profits from sales of RLF-100 for all indications related to COVID-19 and potentially other respiratory indications on a global basis. NRx will lead commercialization (and book sales) in the US, Canada, and Israel, while Relief will lead commercialization (and book sales) in Europe and the rest of the world (ROW). In the US, Canada and Israel, profits will be split on a 50/50 basis. Profits will be split in Europe 85/15 and in ROW 80/20, all in favor of Relief. Both companies will use a value-based pricing model, which will consider the efficacy profile and pharmacoeconomic benefits of RLF-100, in particular the potential impact on mortality. Unfortunately, in April 2021 a pending dispute was announced between Relief and its partner NRx under the Collaboration Agreement, including the refusal to share clinical trial data of the pivotal “COVID-AIV” trial, unpaid clinical trial invoices, the funding of the “AVICOVID-2” trial, stability issues with the formulation of RLF-100. In October 2021, Relief filed a lawsuit in the Supreme Court of the State of New York against NeuroRx and CEO Dr. Javitt alleging breaches in the Collaboration Agreement for the development and commercialization of Relief’s RLF-100. NRx has still not provided all data of the US pivotal “COVID-AIV” phase IIb/III trial necessary for European filings, which has led to delays. Relief and NRx have agreed to hold a mediation to amicably resolve the ongoing litigation between both parties in early January 2022.
RLF-100 included in US “I-SPY COVID-19” a platform trial assessing multiple drugs

In January 2021, NRx and Quantum Leap Healthcare Collaborative (Quantum Leap) signed a clinical trial participation agreement to include RLF-100 INHALED in the “I-SPY COVID-19” clinical trial. The “I-SPY COVID-19 trial is a platform trial assessing multiple drugs for the treatment of patients with critical COVID-19 who are hospitalized or in intensive care units (ICUs). The trial uses a similar protocol as a traditional clinical trial, but compares multiple investigational drugs combined with a “backbone” of the standard of care to rapidly identify those drugs that have a large impact on reducing disease severity, including reduced mortality, reducing or avoiding time on ventilation and other long-term comorbidities. RLF-100 will be included as one of the first drugs targeting respiratory failure in critically ill COVID-19 patients. Quantum Leap is the sponsor of the trial.

RLF-100 IV included in NIH-sponsored phase III “ACTIV-3b/TESICO” COVID-19 trial

RLF-100 IV has also been identified by the National Institutes of Health (NIH) as one of two drugs selected for inclusion in the multicenter phase III trial “ACTIV3b/TESICO” (Therapeutics for Severely Ill In patients with COVID-19) that will include the US and multiple foreign countries. 640 patients will be randomly allocated to RLF-100 IV and Gilead’s Veklury (remdesivir), the combination of both drugs, and placebo. The primary endpoint of the trial will be patient recovery from respiratory failure over 90 days. Three safety updates by the independent DSMB in August, September and November 2021 showed no safety concerns with the trial to continue to enroll patients. The trial is funded by the US Government COVID-19 Therapeutics Response and sponsored by the National Institute of Allergy and Infectious Diseases (NIAID). Topline results are expected in Q4 2022.

Supply chain agreements to provide RLF-100 on a timely basis in the US and Europe

In September 2020, Relief and NRx established supply chain agreements and ordered sufficient drug substance to prepare to treat to treat large number of COVID-19 patients with RLF-100. Bachem Americas and Nephron Pharmaceuticals have been contracted to manufacture commercial supplies of RLF-100 to ensure that adequate drug inventory will be immediately available upon approval. Bachem Americas is a long-time and cost-effective manufacturer of aviptadil API with the ability to scale up rapidly. Nephron Pharmaceuticals will provide the final form “fill/finish” sterile injectable drug product.

In November 2020, Relief appointed Syneos Health (NASDAQ symbol: SYNH), a global clinical research organization (CRO), to run the European phase IIb/III clinical trial, if required, of RLF-100 in COVID-19 induced ARDS, as well as future trials in other indications to be conducted in Europe. Relief also selected AMRI, a global contract and development and manufacturing organization (CDMO), who will provide aseptic final form “fill/finish” sterile injectable formulation RLF-100 at their Glasgow, UK, facility.

In March 2021, NRx announced a collaboration with TFF Pharmaceuticals to determine the feasibility of formulating RLF-100 as a dry powder using TFF Pharmaceuticals’ Thin-Film Freezing (TFF) technology. This could expand the use of RLF-100 beyond an inhaled nebulized formulation to use in a more convenient dry powder inhaler (DPI).

In July 2021, NRx announced it has validated a commercial formulation for RLF-100 IV (aviptadil intravenous formulation) allowing for high volume manufacture with an anticipated one year or greater stability under appropriate storage conditions. Simultaneously, NRx achieved a 30-to-50-fold increase in its manufactured lot size of RLF-100 IV with the potential to deliver millions of doses worldwide and enabling stockpiling. The new
formulation will be used in the ongoing clinical trials and programs, including the NIH-sponsored phase III “TESICO” trial and the phase II “I-SPY-COVID” adaptive platform trial as well as the Expanded Access Program and Right to Try program.

In August 2021, NRx signed an agreement with Cardinal Health to provide third party logistics and distribution of RLF-100 IV upon the potential EUA approval in the US. The partnership creates an efficient and highly flexible logistics and distribution model for NRx. Cardinal Health’s expertise will enable RLF-100 IV to quickly reach patients in the intensive care units where limiting time to treatment is critical. Cardinal Health supplies more than 90% of hospitals in the US and has more than 20 years of experience of supporting rapid delivery of life-saving drugs.

In October 2021, NRx announced they have submitted a revised IND (Investigational New Drug) module on the manufacturing of RLF-100 IV to the FDA containing documentation that Nephron Pharmaceuticals is prepared to supply RLF-100 IV on a commercial scale. NRx also received notification that a European Qualified Person Auditor completed an inspection at a separate manufacturing facility with no adverse findings.

In November 2021, NRx reported the completion of an FDA Manufacturing Information review, without the imposition of any clinical hold, which enables NRx to distribute RLF-100, produced at commercial scale under GMP (Good Manufacturing Practices) for clinical trials and other future purposes. The FDA has now reviewed a GMP manufacturing process at a batch size of 10,000 – 100,000 doses with a current shelf life of 150 days. This new process, helped by Nephron Pharmaceuticals, replaces the handmade, 300 dose batches with a limited shelf life of 62 days. NRx will work together with the FDA to complete CMC (chemistry, manufacturing and controls) review that will be needed for any potential drug approval.

Largest shareholder GEM helps to provide sufficient funding into late 2023
Sufficient funding has been largely provided by GEM Global Yield Fund, LLC, Relief’s largest shareholder with a ~22% equity stake. Recent financings have brought in approximately CHF 68 mn, largely from the Share Subscription Facility (SSF) agreement with GEM, which concluded in September 2020, and approximately CHF 25 mn from two private placements with US institutional investors in March and July 2021. In January 2021, Relief established a new CHF 50 mn SSF with GEM, which it intends to use, if necessary, to fund the purchase of additional commercial supply of RLF-100 to meet demand as needed, as well as pursue further business development opportunities such as with ACER-001 and the APR acquisition.

EAP - Early clinical data supports use in critically ill COVID-19 patients
RLF-100 IV has showed the ability to induce rapid recovery from respiratory failure in the most critically ill COVID-19 patients. The first report of rapid clinical recovery under emergency use IND was posted by doctors from Houston Methodist Hospital in Texas. The report describes a 54-year-old man who developed COVID-19 while being treated for rejection of a double lung transplant and who came off a ventilator within four days. Similar results were subsequently seen in more patients treated under emergency use IND and an FDA Expanded Access Program, which is open to patients who are too ill to be enrolled to the US phase IIb/III “COVID-AIV” trial. Patients with critical COVID-19 were seen to have a rapid clearing of classic pneumonitis findings on X-ray, accompanied by an improvement in
blood oxygen and a 50% or greater average decrease in laboratory markers associated with COVID-19 inflammation.

In October 2020, topline results from 45 patients assessed in an open-label prospective study where 21 patients admitted to an intensive care unit (ICU) with critical COVID-19 and respiratory failure were treated with RLF-100 IV and compared to 24 control patients treated in the same setting. All patients had severe comorbidities that rendered them ineligible for the ongoing randomized, controlled phase IIb/III “COVID-AIV” trial being conducted to assess safety and efficacy of RLF-100 IV, and all patients were deteriorating despite treatment with approved therapies for COVID-19. At the 28-day time point, 90% of RLF-100 IV-treated patients had survived vs. 27% of control patients. At the 60-day time point, 81% of RLF-100 IV-treated patients survived, compared to only 17% of control patients. Those patients treated with RLF-100 IV demonstrated a 9-fold increased probability of survival and recovery from respiratory failure, with a high degree of statistical significance (p<0.0001). These positive results were published in the peer-reviewed “Journal of Infectious Diseases and Treatment” in October 2021.

In late November 2020, Relief and NRx reported additional data from the Expanded Access Protocol (EAP) patient population treated with RLF-100. The companies indicated that over 175 patients with critical COVID-19 and respiratory failure who also have severe comorbidities had been entered into the EAP program – it is now estimated that well over 200 patients have received RLF-100 IV via this program. All patients had severe comorbidities (such as organ transplant, recent heart attack, and cancer) that rendered them ineligible for the ongoing randomized, controlled phase IIb/III “COVID-AIV” trial being conducted to ascertain RLF-100 IV safety and efficacy; all patients were deteriorating despite treatment with approved therapies for COVID-19. Of the 90 patients who had reached 28 days of follow-up as of November 2020, 72% had survived to day 28. The availability of a substantially larger cohort of patients from the EAP program may be considered to partially address concerns pertaining to the lack of a control group or a randomized study design. It should be noted that, as indicated previously, these patients were critically ill and generally had exhausted all pharmacotherapy options. They could not have been enrolled into the phase IIb/III RLF-100 IV clinical trial.

In June 2021, NRx released additional positive results from the RLF-100 IV US Expanded Access Program (EAP). The EAP included 240 intensive care unit (ICU) patients suffering from critical COVID-19 with respiratory failure who had exhausted all approved therapies. The results of the EAP are similar to the results of the pivotal phase II/III “COVID-AIV” trial, which forms the base of the US Emergency Use Application submission in early June. At day 28, 65% of patients receiving RLF-100 IV and maximal intensive care were alive, while survival was higher in patients treated with high flow rate oxygen by nasal cannula (76%) than patients requiring either invasive or non-invasive mechanical ventilation (54%). The EAP data are being submitted by NRx to the FDA as “real world” evidence in support of the findings of the “COVID-AIV” trial.

The clinical findings may be based on evidence that VIP inhibits the replication of the SARS-CoV-2 virus in human lung cells and immune cells (monocytes), as discussed in the pipeline section (see page 20). To date, no other antiviral agent has demonstrated rapid recovery from viral infection and demonstrated laboratory inhibition of viral replication.
Pivotal US phase IIb/III – “COVID-AIV” trial of RLF-100 IV started in June 2020

Based on these promising early results, Relief’s strategic development and commercialization partner NRx started the single potentially pivotal US phase IIb/III “COVID-AIV” trial of RLF-100 IV in patients with COVID-19 induced ARDS in June 2020. Respiratory failure or ARDS is the hallmark of acute COVID-19 infection and is the most critical complication with a high mortality rate due to the lack of effective treatments. Up to 80% of these patients die despite intensive care and mechanical ventilation. Moreover, the number of COVID-19 induced ARDS patients has resulted in an acute shortage of hospital and ICU capacity in many countries, leading to drastic lockdown measures at high economic and social cost.

“COVID-AIV” is a multicentered, randomized, quadruple blind, placebo controlled phase IIb/III trial conducted at 10 hospitals in the US, which enrolled 196 patients with COVID-19 induced ARDS (critical COVID-19 with respiratory failure). Patients currently treated with high flow nasal oxygen, non-invasive ventilation or mechanical ventilation were treated with RLF-100 IV administered intravenously receiving escalating doses from 50 - 150 pmol/kg/hr over 12 hours plus maximal intensive care vs. placebo plus maximal intensive care. Resolution of respiratory failure (without relapse) and survival through the observation period was the prespecified primary endpoint specified by the FDA, originally intended to be assessed at 28 days (as required for ARDS trials) and then extended to 60 days (new requirement for COVID-19 induced ARDS) based on newly published FDA guidance for developing drugs and biological products for treatment and prevention of COVID-19 in February 2021. The 60-day observation framework implemented by the FDA for critically ill patients with COVID-19 is more consistent with the clinical course of this lethal disease than the 28-day time frame originally adapted from other conditions that cause respiratory distress.

Trial enrollment was completed in December 2020, while the trial received two consecutive positive reviews from the Data Monitoring Committee to continue the trial with no drug-related serious events or safety concerns.

Positive 60-day topline results pivotal “COVID-AIV” trial reported end March 2021

At the end of March 2021, NRx reported the 60-day topline results of the pivotal single phase IIb/III “COVID-AIV” trial of RLF-100 IV in critically ill patients with COVID-19. Across all patients and sites, RLF-100 IV met the primary endpoint for successful recovery from respiratory failure at days 28 (p=0.014) and 60 (p=0.013) and also demonstrated a meaningful benefit in survival (p<0.001) after controlling for ventilation status and treatment site. The analysis includes all 196 participants who were randomized and treated in the placebo-controlled, double-blind clinical trial conducted at 10 US hospitals. Treatment with RLF-100 IV or placebo was in addition to standard of care treatment that included steroids, convalescent plasma, antiviral therapy, anticoagulants, and various anti-cytokine drugs.

In addition to the robust overall significance across all 196 treated patients at all 10 clinical sites, the prespecified analysis of recovery from respiratory failure is clinically and statistically significant in the 127 patients treated by High Flow Nasal Cannula (HFNC) (p=0.02), compared to those treated with mechanical or non-invasive ventilation at tertiary care hospitals. In this group, RLF-100 IV patients had a 71% chance of successful recovery by day 28 vs. 48% in the placebo group (p=0.017) and a 75% rate of successful recovery by day 60 vs. 55% in the placebo group (p=0.036). 84% of HFNC patients treated at tertiary...
medical centers with RLF-100 IV survived to day 60 compared with 60% of those treated with placebo (p=0.007).

The association of baseline oxygenation status (high flow nasal oxygen vs. ventilation) is not surprising in that patients who require mechanical or noninvasive ventilation in order to maintain blood oxygen are likely to have substantially more damage to the lining of their lungs compared to patients whose blood oxygen level can be maintained with high-flow oxygen delivered to the nose. The finding that patients fared substantially better in tertiary care centers as compared to regional hospitals may be influenced by the intensity of the public health crisis at the regional hospitals that participated in the study, all of which were operating at 200% or higher overcapacity in their intensive care units with implementation of temporary ICU beds and shortages of critical care staff.

**Data shows RLF-100 IV prevents the dreaded “cytokine storm” in COVID-19**

In July 2021, NRx presented data that identified a statistically significant effect of RLF-100 IV in preventing the sharp rise in cytokines also known as the “cytokine storm” commonly associated with mortality in patients with COVID-19 in the pivotal phase IIb/III “COVID-AIV” trial of RLF-100 IV in critically ill COVID-19 patients with respiratory failure. The data were collected as part of the trial. Patients treated with placebo experienced a statistically significant elevation in interleukin 6 (IL-6) cytokine levels, whereas those treated with RLF-100 IV had a minimal increase in IL-6. Change in cytokine level was a prespecified endpoint of the trial. The effect was noted across a diverse set of patients, suffering different levels of COVID-19 severity and treated in both tertiary care and community hospitals. NRx has submitted these findings to the FDA as a supplement to its pending application for EUA and is submitting a biomarker letter of intent to the FDA as part of its biomarker program, authorized under the 21st Century Cures Act. NRx continues to respond to FDA information requests for additional data in support of the currently pending EUA application for RLF-100 IV in treating critically ill patients with COVID-19.

**US EUA declined by FDA pushing back potential US approval by roughly a year**

RLF-100 IV is likely the first COVID-19 therapeutic to demonstrate advantages in both survival and recovery from critical COVID-19 in a randomized, double-blind multicenter trial. On the basis of these findings, NRx applied to the FDA for Emergency Use Authorization (EUA) on 31 May 2021, and to subsequently submit a New Drug Application (NDA). On 4 November 2021, the FDA declined to issue Emergency Use Authorization (EUA) for RLF-100 IV for the treatment of acute respiratory failure due to critical COVID-19. The FDA stated that it was unable to issue the EUA at this time due to insufficient data regarding the known and potential benefits of the medicine and the known and potential risks of RLF-100 IV in patients suffering from critical COVID-19 with respiratory failure. In its letter, the FDA noted that so far, it has reviewed safety in only 131 randomized patients treated with RLF-100 IV.

NRx states that it will attempt to coordinate a review by the FDA of the 150 or more additional patients already treated with RLF-100 IV in the NIH-sponsored ACTIV-3b/TESICO trial. The trial has enrolled more than 300 patients of the targeted 640 patients with three positive safety reviews by the independent DSMB. According to clinicaltrials.gov, the primary completion date of the ACTIV-3b/TESICO trial is October 2022, when topline results should be reported. We do not fully understand how NRx will attempt a review by the FDA of the more than 150 patients enrolled as the trial is still actively enrolling and blinded, which would compromise the final results. Therefore, we believe the filing of a new US EUA can only occur after the topline results of the ACTIV-3b/TESICO have been announced in Q4 2022,
leading to roughly a year’s delay for a potential US approval for RLF-100 IV in treating COVID-19 related ARDS. Assuming the FDA grants an EUA, first commercial sales in the US could be expected in around year-end 2022, which would be transformational for Relief.

**Potential EU approval also pushed back by roughly a year into H1 2023**

Following US EUA, it is likely that the EMA would also grant Conditional Marketing Authorization (CMA) for RLF-100 IV to treat these critically ill COVID-19 patients. Relief plans to file for EU CMA following a potential US EUA grant in around year-end 2022. This could result in first EU commercial sales to start in H1 2023. Relief has secured API supply of up to 1 mn doses of RLF-100 IV with Bachem Americas. Relief expects that a small sales organization should be sufficient to successfully commercialize RLF-100 IV in the US and EU. The drug is targeted to be used by a relatively small number of respiratory medicine and critical care/ICU specialists and administered intravenously in a healthcare setting where critically ill patients are being treated.

**Commercial potential of RLF-100 dependent on the success of COVID-19 vaccines**

The commercial potential of RLF-100 in COVID-19 respiratory complications will be highly dependent on 1) the efficacy of RLF-100 IV on reducing mortality, morbidity and treatment duration freeing up scarce hospital and ICU capacity; 2) the trajectory of the ongoing COVID-19 pandemic; 3) emerging new treatments for critically ill COVID-19 patients; 4) the timing of approval, pricing and reimbursement and commercial rollout, among others. We will discuss in more detail below.

**Efficacy of RLF-100 in reducing mortality**

RLF-100 IV is likely the first COVID-19 therapeutic to demonstrate advantages in both survival and recovery from critical COVID-19 in a randomized, double-blind multicenter trial. This should justify rapid approval, premium pricing, a sharp commercial uptake and large pandemic stockpiling orders across the globe. This would be transformational for Relief.

**Trajectory of the COVID-19 pandemic – Global vaccination programs having impact**

Broadscale and effective vaccination of the population combined with social distancing and lockdown measures will be key to contain the COVID-19 pandemic. Early in the year vaccination rates were severely lagging initial projections due to a short supply of vaccines and the complicated logistics involved in setting up and executing large scale vaccination programs prioritizing high-risk patients (elderly, additional comorbidities) and care givers. Vaccination rates in the high-income countries have increased significantly over the last few months with most high-risk patients fully vaccinated, resulting in significantly lower COVID-19 hospitalizations and critically ill patients treated in the ICU.

In most high-income countries, it is likely to take until early 2022 before a sufficient number of people are vaccinated to provide the necessary herd immunity to make a lasting impact on the COVID-19 pandemic. Several factors are expected to impact the trajectory of global COVID-19 infections, including:

**COVID-19 virus mutations:** It is not unusual for a virus to mutate and evolve as it spreads, and scientists have long cautioned that other worrisome variants could emerge with new outbreaks. The emergence of mutations of the SARS-CoV-2 virus with significantly higher transmission rates makes keeping the virus from spreading a lot harder than in 2020. Currently, a more contagious variant of the coronavirus, known as delta, is spreading around the world, causing a surge of cases in some
countries and prompting several nations to introduce new lockdowns. The delta variant has been reported in more than 95 countries, according to the World Health Organization (WHO). The delta variant, which was first identified in India, now accounts for 25% of new COVID-19 cases in the US and is on track to become the dominant version of the virus circulating, according to the Centers for Disease Control and Prevention (CDC). Research suggests that delta, officially known as B.1.617.2, is the most contagious of all the known variants to date, including the highly transmissible alpha variant that was first identified in the UK. Public health officials in the UK, where delta accounts for more than 95% of new COVID-19 cases, have said that the variant could be 40 to 60 percent more transmissible than the alpha variant.

The vaccines in use in high income countries (see below) appear to offer good protection against the delta variant, and most scientists agree that fully vaccinated individuals likely face little risk. In the unlikely scenario that mutations significantly lower a vaccine’s efficacy, it would take four to six weeks to develop a modified vaccine. Whereas the pandemic’s trajectory in 2020 was fairly predictable, the evolution of the virus makes containment harder and the trajectory of the pandemic more unpredictable. It is also possible that the more contagious strains of the SARS-CoV-2 coronavirus spread so rapidly that they outstrip the pace at which vaccines can be deployed. Some of the newer strains may also prove capable of evading the immune protection elicited by vaccination, resulting in a game of cat and mouse with modified vaccines.

For instance, in June 2021 the newly assigned SARS-CoV-2 lineage C.37 was recently classified as a variant of interest by the WHO and denominated as the Lambda variant. The presence of this new variant has been reported in more than 20 countries with most of the available sequences coming from South American countries, particularly from Chile, Peru, Ecuador and Argentina. Mutations present in the spike protein of the Lambda variant appear to have increased infectivity and immune escape from neutralizing antibodies elicited by the Chinese Sinovac vaccine CoronaVac (not used in high income countries). These data reinforce the idea that massive vaccination campaigns in countries with high SARS-CoV-2 circulation must be accompanied by strict genomic surveillance allowing the identification of new isolates carrying spike mutations and immunology studies aimed to determine the impact of these mutations in immune escape and vaccines breakthrough.

Vaccine rollout: Vaccine development proceeded at record pace in 2020. This year will be all about the rollout. Pfizer/BioNTech’s BNT162b, Moderna’s mRNA-1237 and AstraZeneca’s AXD1222 are among the first COVID-19 vaccines to be approved and launched. These vaccines require two separate shots within ~3-4 weeks to provide the claimed high efficacy of around 95% (and around 76% for AXD1222). Pfizer/BioNTech’s vaccine needs to be stored at -70°C, providing an advantage for Moderna’s vaccine that can be stored at lower temperatures. Recently, AstraZeneca and Pfizer/BioNTech experienced manufacturing problems with a significant shortfall in promised vaccine supplies to several countries. AstraZeneca’s vaccine continues to be hampered with safety considerations, in particular with regards to very rare cases of unusual blood clots associated with low blood platelets. Several countries have stopped using the drug or have limited use to people aged 65 and older.
Some later entrants hope to offer more convenient dosing schedules such as Johnson & Johnson’s recently approved single-shot COVID-19 vaccine, which can be kept at regular refrigerator temperatures and effective against moderate to severe/critical COVID-19 in South Africa and Latin American variations. In the US, it is considered 72% effective and offered 86% protection against severe forms of the disease. With efficacy around 95%, Pfizer/BioNTech and Moderna’s vaccines have set an incredibly high bar; few would swallow a convenience advantage if it came with a significant compromise on protection. Unless those coming behind get pivotal studies up and running fast, recruitment will surely become harder, as will generating data, since the first vaccines will hopefully swiftly suppress the virus. If infection rates start to drop sharply, this year could see a number of developers drop out of the running entirely.

Vaccine duration of protection: One big unknown regarding all the COVID-19 vaccines is the duration of protection against the coronavirus. In the case of currently approved COVID-19 vaccines, measures of neutralizing antibody levels have been strong weeks after immunization. But it is too early to tell whether these antibody levels will remain strong for at least a year. If immunity to SARS-CoV-2 by vaccination is not long-lasting or permanent, the virus will likely enter into regular circulation, much like pandemic influenza. Regular global vaccination programs will be necessary requiring booster shots in portions of the population, especially in the older, more vulnerable population such as immunocompromised patients and adults with severe pre-existing medical conditions. Little information is available on whether the available COVID-19 vaccines will provide sufficient protection against new rapidly emerging mutations. If immunity to SARS-CoV-2 is permanent, the virus could disappear for 5 or more years after causing a major outbreak. A sufficiently high vaccination rate of 70-80% in the general population must be attained, too.

Anti-vaccine sentiment: Increased populism and distrust in science combined with the spread across social media platforms have led to increased anti-vaccine sentiment in the US and the EU. In the past, there was already an increasing mistrust in vaccination programs. For instance, in early 2000 there were false claims that vaccines for measles, mumps and rubella had the ability to cause autism, which were only debunked in a Lancet article in 2010. Around 2014/2015, the political far right in the US started an agenda pushing for “health/medical freedom” distrusting government agencies such as the National Institutes of Health (NIH), the CDC or the FDA. Increasing anti-vaccine sentiment may lead to a sizeable portion of the population not being vaccinated, forming a new pool of infection or mutations that could spread through the general population.

COVID-19 pandemic will not end overnight and is expected to persist for some time
Vaccines will be instrumental in the control of the COVID-19 pandemic, but their global distribution remains challenging, and their effect will not be immediate. As cases and deaths continue to rise across the world, non-pharmaceutical interventions such as lockdowns or social distancing measures to constrain the spread of COVID-19 will need to remain in place for a while longer. In a recent “Nature” poll, 89% of scientists felt that the SARS-CoV-2 pandemic was either very likely or likely to become an endemic virus. In the endemic phase, the number of infections becomes relatively constant across years, allowing for occasional flare-ups. To reach this steady state could take a few years or decades, depending on how quickly populations develop immunity. In particular, the continual emergence of new
coronavirus variants that may be immune or more resistant to current vaccines pose a risk. Consequently, the need for new safe and effective treatments for COVID-19 patients is expected to persist for many years to come.

Ultimately, COVID-19 is believed to become endemic and stay around for quite some time with still tens of thousands of critically ill patients hospitalized or in ICUs each year, similar to the influenza virus. As a reference, the annual disease burden of influenza in the US, according to the CDC, amounts to 9.3-45.0 mn influenza cases; 140,000-810,000 hospitalizations; 12,000-61,000 deaths (the top range of these burden estimates are from the 2017-2018 flu season). Patients with COVID-19 have almost 19 times the risk for ARDS than patients with influenza. The percentage of COVID-19 patients who died while hospitalized (21.0%) was more than five times that of influenza patients (3.8%), while the duration of hospitalization was almost three times longer for COVID-19 patients.

**Effective COVID-19 treatments still needed even in the case of effective vaccines.** Despite the global rollout of effective COVID-19 vaccines, these vaccines will not cure patients suffering from COVID-19 symptoms as we discussed earlier. Once the virus has invaded the respiratory system of a patient, a vaccination is of little help. Therefore, new COVID-19 treatments are needed in addition to effective vaccines, and they are needed now to treat critically ill COVID-19 patients and save lives as well as early-intervention treatments to reduce disease progression, treatment times and costs. As the development of novel drugs can take more than 10 years from research to market, the pharmaceutical industry tried to repurpose existing drugs. But many of them showed no significant benefits so far, with some even worsening the patient’s condition. Some current approaches to treat COVID-19 patients, include:

**Antivirals among the first products to be approved – Paxlovid takes the lead**
Antiviral drugs are prescription medicines (pills, liquid, an inhaled powder, or an intravenous solution) that fight against viruses in the body. In May 2020, Gilead’s intravenous infusion Veklury (remdesivir) was the first product approved to treat COVID-19 but clinical evidence that has emerged since shows the antiviral leaves much room for improvement. Oral antivirals such as Pfizer’s Paxlovid (PF-07321332) or Merck & Co’s Lagevrio (molnupiravir) are amongst the most promising treatments in the fight against the global pandemic. Pivotal trials of both drugs were stopped early due to strong positive topline results seen during the planned interim analyses. Pfizer’s Paxlovid appears to have become the most promising new oral antiviral treatment in the fight against the global pandemic cutting the risk of hospitalization or death by almost 90% in hospitalized high-risk adults with COVID-19 infection compared to around 50% for Merck & Co’s Lagevrio. Both treatments are expected to be granted US EUA by year-end and rolled out globally. The US government has already secured millions of doses of both drugs.

**Pfizer’s Paxlovid reduces the risk of hospitalization or death by almost 90%**
Pfizer’s oral antiviral PF-07321332 (branded Paxlovid) is a specifically designed SARS-CoV-2-3CL protease inhibitor given in combination with a low dose of the older HIV antiviral ritonavir (branded Norvir by AbbVie) consists of three pills given twice daily. Paxlovid, significantly reduced hospitalization and death, based on an interim analysis of the phase II/III “EPIC-HR” trial of non-hospitalized adult patients with COVID-19, who are at high risk of progressing to severe illness. The scheduled interim analysis showed an 89% reduction in risk of COVID-19-related hospitalization.
or death from any cause compared to placebo in patients treated within three days of symptom onset (primary endpoint); 0.8% of patients who received Paxlovid were hospitalized through Day 28 following randomization (3/389 hospitalized with no deaths), compared to 7.0% of patients who received placebo and were hospitalized or died (27/385 hospitalized with 7 subsequent deaths). The statistical significance of these results was high (p<0.0001). Similar reductions in COVID-19-related hospitalization or death were observed in patients treated within five days of symptom onset; 1.0% of patients who received Paxlovid were hospitalized through Day 28 following randomization (6/607 hospitalized, with no deaths), compared to 6.7% of patients who received a placebo (41/612 hospitalized with 10 subsequent deaths), with high statistical significance (p<0.0001). In the overall study population through Day 28, no deaths were reported in patients who received Paxlovid as compared to 10 (1.6%) deaths in patients who received placebo.

The primary analysis of the interim data set evaluated data from 1,219 adults who were enrolled by September 29, 2021. At the time of the decision to stop recruiting patients by the independent Data Monitoring Committee, enrollment was at 70% of the 3,000 planned patients from clinical trial sites across North and South America, Europe, Africa, and Asia, with 45% of patients located in the United States. The review of safety data included a larger cohort of 1,881 patients in EPIC-HR, whose data were available at the time of the analysis. Treatment-emergent adverse events were comparable between Paxlovid (19%) and placebo (21%), most of which were mild in intensity. Among the patients evaluable for treatment-emergent adverse events, fewer serious adverse events (1.7% vs. 6.6%) and discontinuation of trial drug due to adverse events (2.1% vs. 4.1%) were observed in patients dosed with Paxlovid compared to placebo, respectively. Pfizer submitted the positive interim results as part of its ongoing rolling submission to the FDA in November 2021 with a US EUA grant likely before year-end.

**Merck’s Lagevrio filed for EUA in mild-to-moderate COVID-19**

Merck & Co’s oral antiviral molnupiravir (branded Lagevrio) was licensed from the privately held Ridgeback Therapeutics. In October 2021, Merck & Co and Ridgeback announced the submission of an Emergency Use Authorization (EUA) application to the FDA for Lagevrio for the treatment of mild-to-moderate COVID-19 in adults who are at risk for progressing to severe COVID-19 and/or hospitalization. An FDA Advisory Committee is set to review Lagevrio on 30 November 2021. The EUA submission is based on positive results from a planned interim analysis from the phase III “MOVE-OUT” clinical trial, which evaluated Lagevrio in non-hospitalized adult patients with mild-to-moderate COVID-19 who were at risk for progressing to severe COVID-19 and/or hospitalization. At the planned interim analysis, Lagevrio reduced the risk of hospitalization or death by approximately 50%; 7.3% of patients who received Lagevrio were either hospitalized or died through Day 29 following randomization (28/385), compared with 14.1% of placebo-treated patients (53/377); p=0.0012. Through Day 29, no deaths were reported in patients who received Lagevrio, as compared to 8 deaths in patients who received placebo. The incidence of any adverse event was comparable in the Lagevrio and placebo groups (35% and 40%, respectively). The incidence of drug-related adverse events was also comparable (12% and 11%, respectively), and fewer subjects in the Lagevrio group discontinued therapy due to an adverse event compared to the placebo group (1.3% and 3.4%, respectively).
Note that Paxlovid and Lagevrio are not for use in late-stage or hospitalized patients and most likely must be administered within five days (or less) of infection to have a meaningful benefit. The lack of long-term safety data concerning Lagevrio and the likelihood of mutagenicity, potentially causing birth defects or cancer could likely result in a black box warning, which would hamper widespread use in its target population.

**Atea and Roche’s AT-527 fails “MOONSONG” phase II COVID-19 trial**

In October 2021, Atea Pharmaceuticals and Roche’s oral direct-acting antiviral AT-527 failed to achieve its primary endpoint of reduction from baseline in the amount of SARS-CoV2 virus in patients with mild to moderate COVID-19 compared to placebo in the phase II “MOONSONG” trial. Approximately two thirds of the overall trial population were low-risk patients with mild symptoms. However, in high-risk patients with underlying health conditions, a sufficient viral load reduction was observed in AT-527 treated patients compared to placebo. In November, Roche ended the partnership with Atea to jointly develop AT-527 in COVID-19.

**Authorized antibodies underutilized due to complex administration issues**

SARS-COV-2-targeting monoclonal antibodies (MAbs) are laboratory-produced antibodies that can help the immune system's attack on COVID-19. These MAbs block entry into human cells, thus neutralizing the virus. The following MAbs are authorized for use through an FDA EUA for the treatment of mild to moderate COVID-19 in adults and pediatric patients who are at high risk for progressing to severe COVID-19 and/or hospitalization:

- **REGEN-COV2 (casirivimab & imdevimab combo):** EUA cleared November 2021 from Regeneron/Roche; IV infusion
- **Sotrovimab:** EUA cleared May 2021 from GlaxoSmithKline/Vir; IV infusion
- **bamlanivimab & etesevimab combo:** EUA cleared February 2021 from Eli Lilly; IV infusion

With three MAbs now available under Emergency Use Authorizations in the US, it seems clear that monoclonal antibodies (MAbs) have a role to play in treating COVID-19. The extent to which they will be helpful is not yet known. However, these products have failed to show a benefit in severely ill patients. While clinical trials are still ongoing, the data so far indicate they are particularly beneficial for certain patients with mild or moderate symptoms whose own immune systems are not mounting a strong defense. Clinical evidence supporting each drug is not yet conclusive. On 25 June 2021, a pause on the distribution of bamlanivimab & etesevimab in the US was issued. Results from in vitro assays that are used to assess the susceptibility of viral variants to particular MAbs suggest that the bamlanivimab & etesevimab combo is not active against either the P.1 (Gamma variant first identified in Brazil) or B.1.351 (Beta variant first identified in South Africa) SARS-Cov-2 variants.

These MAbs have not been widely used since the FDA cleared these products. The limitations of these MAbs have become clear as they have been rolled out. They must be infused in a healthcare setting, raising the risk that infected patients could endanger others at a hospital or a clinic. They are only authorized for patients at high risk of becoming hospitalized, a group the FDA has defined by age and certain underlying health conditions. Furthermore, the MAbs have to be given early in the
disease course requiring fast testing and administration to get the right patients treated at the right time. A more convenient subcutaneous injection (sc) of REGEN-COV2 is being developed, which could be on the market soon to improve access and patient compliance. In April 2021, a phase III trial with REGEN-COV2 sc reduced the risk of symptomatic COVID-19 infections by 81% and the overall risk of progressing to symptomatic COVID-19 by 31%.

In January 2021, the US government agreed to pay as much as USD 2.6 bn for up to 1.25 mn additional doses of Regeneron’s REGN-COV2. This comes on top of a previous agreement to buy 300,000 doses for USD 450 mn in July 2020. It values each dose at USD 2,080, up from USD 1,500 a dose in the earlier round.

**FDA rejects Humanigen’s lenzilumab and CytoDyn’s leronlimab for EUA**

Two investigational MAbs were recently rejected by the FDA for EUA in COVID-19. In May 2021, CytoDyn’s leronlimab was rejected by the FDA citing that the data currently available do not support the clinical benefit of leronlimab for the treatment of COV1D-19. In September 2021, Humanigen’s lenzilumab was also rejected. The FDA noted that it was not able to conclude the known and possible benefits of lenzilumab outweigh the known and potential risks of its use as a COV1D-19 therapy. The FDA invited the companies to present further data when it becomes available.

With complex administration schedules and what will presumably be big price tags, it is hard to see these MAb therapies playing a major role outside of wealthier regions.

**Authorized immune modulators**

Immune modulators are a category of drugs that help activate, boost, or suppress the immune function. In the case of COV1D-19 infection, the immune system can become hyperactive which may result in worsening of disease. Immune modulators can help suppress this hyperinflammation. The following immune modulators are authorized for use through an FDA EUA for the treatment of certain patients with COV1D-19:

- **Olumiant (baricitinib):** EUA cleared November 2020 from Eli Lilly; an oral immune modulator in combination with Gilead’s Veklury (remdesivir) for treatment of hospitalized adults and pediatric patients (2 years or older) and requiring supplemental oxygen, invasive mechanical ventilation (IVM) or extracorporeal membrane oxygen (ECMO)
- **Actemra (tocilizumab):** EUA cleared June 2021 from Roche/Genentech; is a MAb available as an IV infusion or subcutaneous injection that reduces inflammation by blocking the interleukin (IL)-6 receptor for the treatment of hospitalized adults and pediatric patients (2 years or older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or IVM or ECMO. Actemra is FDA-approved for the treatment of multiple inflammatory diseases, including rheumatoid arthritis.

Finally, several trials of repurposed drugs could yield results in 2021. JAK inhibitors remain a mechanism of interest, with two industry-sponsored trials due to read out from Incyte and Lilly.
CHF 200 mn global peak sales in COVID-19 induced ARDS with first launches in 2023

We have based our detailed bottom-up forecasts for RLF-100 largely on detailed data available in the US and extrapolated the data where possible to other regions, where detailed data is often lacking or not publicly available. We have based our estimates on sources such as COVID-NET, NCBI, NIH, CDC, WHO, AAAS, ERS, ATS, The Lancet, clinicaltrials.gov and Evaluate Pharma, among others. To account for regional differences, we provide detailed forecasts for the US, Europe and ROW (stockpiling orders only). We forecast until US formulation patent expiry of RLF-100 IV (including 5-year Hatch Waxman patent extension) in 2034. In the US, RLF-100 IV will also enjoy 5 years of New Chemical Entity (NCE) exclusivity following formal NDA approval (during which no generic introduction shall be possible) and potentially 7 years of Orphan Drug exclusivity for acute lung injury (ALI) including ARDS. We conservatively exclude Orphan Drug exclusivity for ALI as the number of COVID-19 induced ARDS patients is likely too high to qualify as an orphan disease. In Europe, we anticipate generic versions of RLF-100 IV to enter the market after EU formulation patent expiry in 2026. Note: in this report, we only provide 10-year forecasts for each indication of RLF-100 due to space considerations.

Detailed bottom-up forecasts point to CHF 120 mn peak sales in COVID-19 ARDS

In 2020, there were 20.2 mn confirmed COVID-19 cases of which 3.9% of critical patients were hospitalized. An estimated 33% of patients had ARDS of which ~90% were transferred to the ICU and approximately 75% received High Flow Nasal Cannula (HFNC). Of these patients we believe ~90% are eligible for treatment with RLF-100 IV. In 2020, the number of eligible patients with COVID-19 induced ARDS for treatment with RLF-100 IV would amount to almost 160,000 patients.

In 2023, we assume an average of 80% of the population fully vaccinated with a 33% drop in the number of COVID-19 cases. The following years we expect the number of COVID-19 cases to continue to decline but still expect a large number of the population to be affected by COVID-19, similar to the seasonal influenza.

Assuming an EUA for RLF-100 in the US around year-end 2022, we expect rapid and substantial uptake of RLF-100 IV in the target population. Peak sales for COVID-19 induced ARDS in 2023 are expected to amount to CHF 120 mn, assuming a USD 9,000 cost of treatment course per patient and a 45% penetration rate. US sales will be booked by partner NRx. M&S costs are expected to be relatively low at approximately USD 10 mn with only a few large buyers. Relief is entitled to 50% of the profits from sales of RLF-100 IV in the US.

European sales to peak at approximately CHF 60 mn in 2023

For Europe, we apply the same approach as for the US and assume a similar decline of COVID-19 cases. EU conditional approval could follow shortly after a potential US EUA grant with launch to occur in H1 2023. We expect RLF-100 IV to reach peak sales of CHF 59 mn in COVID-19 induced ARDS in 2023, with a 40% peak penetration rate and a cost of treatment course per patient of EUR 4,000. Beyond 2023, we assume a similar decline in the number of COVID-19 cases and a similar penetration rate as in the US. In Europe, Relief books sales, and accounts for COGS and M&S costs, with NRx entitled to 15% of the profits.

In the ROW territories, we only account for pandemic stockpiling in 2023 and 2024. We conservatively assume 50,000 treatment courses for each year at a cost of USD 500 per treatment course resulting in CHF 23 mn for each year (for details see the following page).
## RLF-100 IV - FINANCIAL RESULTS FOR COVID-19 INDUCED ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

### RECOMMENDATION
REDUCTION OF MORTALITY AND MORTALITY IN PATIENTS WITH COVID-19 INDUCED ACUTE RESPIRATORY DISTRESS SYNDROME

### DOSE
ONE OR MORE ESCALATING DOSES FROM 50-150 MG/HR INTRAVENOUS ADMINISTRATION OVER 12 HOURS OVER A COURSE OF A WEEK

### PRICE
COST TREATMENT COURSE PER PATIENT: US ($150,000); EU ($200,000); COVID-19 ARDS: EU: $5,000; ASIA: $5,000; ROW: $5,000

### STANDARD OF CARE
PERSONALIZED LONG-PROTECTIVE MECHANICALLY VENTILATION COMBINED WITH GILEAD'S VAPIRIL (REMDEMIVIR) OR TERICIDES SUCH AS DEXAMETHASONE

### UNIQUE SELLING POINT
PETITION: POTENTIALLY FIRST TREATMENT TO REDUCE HIGH MORTALITY AND MORTALITY IN PATIENTS WITH COVID-19 INDUCED ACUTE RESPIRATORY DISTRESS SYNDROME

## 7% ANALYSIS
**PATIENT**
US PATENT EXPIRY 2025; 5-YEAR HATCH-WAXMAN EXTENSION; 5 YEARS NCE EXCLUSION; EU: PATENT EXPIRY 2026; ODD ARDS (COVID-19 ARDS LIKELY NOT ORPHAN)

**PHASE**
US PHASE I/II/III "COVID-19" POSITIVE 60-DAYS TRIAL RESULTS MARCH 2021; US: EUA Q3 2022; EU: EULIG Q1 2023; EU: EMA APPROVAL Q2 2023

**PATHWAY**
POSITIVE "COVID-19" RESULTS LIKELY TO TRIGGER EMERGENCY USE AUTHORIZATION; EU: EMERGENCY APPROVAL LIKELY TO TRIGGER "COVID-19" TRIALS HIGHER LIKELIHOOD TO SURVIVE HOSPITALIZATION WITH LESS COMPLICATIONS AND HOSPITAL DAYS THAN CURRENT INEFFICIENT TREATMENT OPTIONS

**PHYSICIAN**
FIRST SAFE AND EFFECTIVE TREATMENT TO SIGNIFICANTLY REDUCE MORTALITY AND MORTALITY FOR PATIENTS WITH COVID-19 OTHERWISE POOR PROGNOSIS

**PAYOR**
SIGNIFICANTLY REDUCES OVERALL TREATMENT COSTS WITH MORE CRITICAL PATIENTS SURVIVING WITH LESS DAYS SPENT IN ICU OR HOSPITAL WITH LESS COMPLICATIONS

**PARTNER**
NEUROLOGY COMMERCIALIZES IN US, CANADA & IRISH; RELIEF IN EUROPE & ROW; PROFIT SPLIT RELIEF/NURSING, US: CANADA & IRISH: $100; EUROPE: $500; ROW: $200

### REVENUE MODEL

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<th>2022E</th>
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### REVIEWS

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<td>94%</td>
<td>93%</td>
<td>92%</td>
<td>91%</td>
<td>90%</td>
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### SUCCESS PROBABILITY

- **CAD-004**: 70% (P2)
- **CAD-005**: 70% (P2)
- **CAD-006**: 70% (P2)
- **CAD-007**: 70% (P2)
- **CAD-008**: 70% (P2)
- **CAD-009**: 70% (P2)
- **CAD-010**: 70% (P2)

### RISK ADJUSTED NPV PER SHARE (CHF)

- **CHF 0.030**

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**SOURCE:** VALUATIONLAB ESTIMATES

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Please see important research disclosures at the end of this document.
Prevention COVID-19 related ARDS second major COVID-19 indication for RLF-100

Prevention of COVID-19 related ARDS is another major complication of COVID-19 infection. These are COVID-19 patients with moderate to severe respiratory complications who are at risk to progress to critical respiratory failure. Relief is first developing RLF-100 IV in treating critically ill COVID-19 patients with respiratory failure, followed by preventing worsening of patients at risk of developing critical COVID-19 respiratory failure with RLF-100 INHALED. This is a clinical development strategy we often see with cancer drugs. Clinical development is initially started in cancer patients with advanced disease and, if this is successful, earlier stages of disease with higher patient numbers are targeted to maximize the target population where the drug is potentially effective. Moreover, treatment duration is significantly longer in patients with moderate to severe disease than patients with critical or advanced disease.

Prevention of critical respiratory failure frees up scarce hospital and ICU capacity

Preventing COVID-19 patients with moderate to severe respiratory symptoms from progressing to critical respiratory failure with RLF-100 INHALED has major advantages. Prevention significantly reduces the number of patients being hospitalized, hence, the number of patients developing critical ARDS, which often results in death or costly long-term complications and negatively affects quality of life. Drugs that can successfully prevent the onset of critical respiratory failure have the potential to significantly reduce overall treatment costs and most importantly free up scarce hospital and ICU capacity with the potential to scale down dreaded lockdown measures with a high economic and social cost.

Authorized MAbs not ideal for treating patients with mild to moderate symptoms

The three authorized monoclonal antibodies (MAbs) from Regeneron (REGN-COV2), Eli Lilly (bamlanivimab) and GlaxoSmithKline/Vir (sotrovimab) have not been widely used since cleared by the FDA. They have failed to show a benefit in severely ill patients. While clinical trials are still ongoing, the data so far indicate they are particularly beneficial for certain patients with mild or moderate symptoms whose own immune systems are not mounting a strong defense. The limitations of both drugs have become clear as they have been rolled out. They must be infused in a healthcare setting, raising the risk that infected patients could endanger others at a hospital or a clinic. They are only authorized for patients at high risk of becoming hospitalized, a group the FDA has defined by age and certain underlying health conditions. Also, the MAbs have to be given early in the disease course requiring fast testing and administration to get the right patients treated at the right time.

RLF-100 INHALED has several advantages compared to MAbs

We believe the major advantage that RLF-100 INHALED has compared to current authorized MAbs is its less cumbersome route of administration. RLF-100 INHALED can be given in an outpatient (home) setting being an inhaled formulation of RLF-100, which can be inhaled via mesh nebulizer three times a day. MAbs have to be administered intravenously in an inpatient (hospital/clinic) setting by trained professionals. This also raises the risk that infected patients could endanger others at a hospital or a clinic. RLF-100 has been demonstrated to be safe and well tolerated with significantly lower COGS vs. MAbs, thus providing substantially more pricing flexibility. Finally, NRx, in collaboration with TFF Pharmaceuticals, is exploring the feasibility of formulating RLF-100 as a dry powder using its Thin-Film Freezing (TFF) technology, which would expand use in convenient dry powder inhalers (DPIs). In August 2021, NRx signed an agreement with MannKind Corporation to
develop a dry powder inhaler formulation of RLF-100 based on its Technosphere platform, that is the basis of its FDA approved inhaled insulin compound branded Afrezza. This potentially allows to extend the use of RLF-100 to many pulmonary conditions beyond COVID-19.

**US phase IIb/III “AVICOVID-2” data in prevention COVID-19 related ARDS due H1 2022**

In February 2021, Relief’s partner NRx started the single potentially pivotal US phase IIb/III “AVICOVID-2” trial in COVID-19 patients with early signs of respiratory distress who will be given RLF-100 INHALED in the hope of preventing progression to ARDS and the need for mechanical ventilation. The multicenter, randomized, quadruple blind, placebo controlled phase IIb/III trial is expected to enroll 288 subjects, 144 hospitalized and 144 treated in an at home-setting with diagnosed COVID-19 infection but no evidence of ARDS. RLF-100 will be inhaled by mesh nebulizer 3 times daily at 100 µg per dose for the time of hospitalization. The primary endpoint is progression to ARDS at 28 days. Progression to ARDS is defined as the need for mechanical ventilation. Results of the US “AVICOVID-2” trial are due in H1 2022. On positive results, RLF-100 INHALED is expected to be approved and launched in the US in 2022.

**Phase II trial RLF-100 INHALED in prevention COVID-19 related ARDS started in April**

In April 2021, Relief, and partner AdVita announced the start of a phase II trial of RLF-100 INHALED for the prevention of COVID-19 related ARDS. The phase II trial is a randomized, double blind, placebo-controlled trial conducted at several clinical sites in Switzerland. 80 patients are expected to be enrolled who will receive either RLF-100 INHALED plus standard of care treatment or placebo plus standard of care treatment. The primary endpoint is the time (in days) from hospitalization to clinical improvement, up to day 28. Clinical improvement is defined as either alive hospital discharge or a decrease of two or more points on the WHO-recommended nine-point ordinal scale of clinical status (WHO, 2020). AdVita is providing all relevant documentation, financial support with the aid of Relief, and study drug for the trial. The trial is estimated to take approximately 6-12 months to complete, depending on the progression of the ongoing COVID-19 pandemic.

**CHF 500+ mn global peak sales in prevention of COVID-19 related ARDS**

Like RLF-100 IV in COVID-19 induced ARDS, we have based our bottom-up forecasts for RLF-100 INHALED in prevention of COVID-19 related ARDS largely on detailed data available in the US and extrapolated the data where possible to the EU, where detailed data is often lacking or not publicly available. We have based our estimates on the same sources. To account for regional differences, we provide detailed forecasts for the US and Europe. In the US, we forecast sales until formulation patent expiry (including 5 years of Hatch Waxman patent extension) until 2034. In Europe, we conservatively forecast generic versions of RLF-100 INHALED to enter the market after the formulation patent expires in 2026. We assume the same decline in the number of COVID-19 cases in the US and EU as we do for RLF-100 IV in COVID-19 ARDS.

**US peak sales to reach more than CHF 360 mn in 2023**

Roughly 50% of people infected with COVID-19 infection experience symptoms. Of these symptomatic patients almost 80% have respiratory complications. An estimated 55% have mild respiratory symptoms, approximately 30% have moderate symptoms ~10% severe symptoms, and ~5% are critical. Of the 30% patients with moderate respiratory symptoms, almost 38% of patients are in a recovery phase with lung impairment and are at risk of developing life-threatening ARDS. Most of these patients can be treated at home. We
assume, RLF-100 INHALED could reach up to a 20% peak penetration in these patients. Approximately 90% of patients with severe respiratory complications are in a recovery phase with lung impairment, with many still hospitalized. We assume that RLF-100 INHALED could reach peak penetration rates up to 40%. Assuming a treatment cost of USD 10,000 per patient, patient compliance of 90% and US launch in 2022, peak sales in the US are forecast to reach more than CHF 360 mn in 2023 and gradually decline as the COVID-19 pandemic becomes endemic due to the ongoing vaccination programs. Relief has identified distribution channels for RLF-100 INHALED with more to be added in the future.

**CHF 200 mn peak sales in Europe with patent protection only until 2026**

For Europe we apply the same approach as for the US. We assume first launches in 2023. Peak sales in Europe are expected to amount around CHF 200 mn in 2024 and gradually decline due to the decline in the number of COVID-19 cases. Peak sales in Europe are lower than the US due to the lower number of COVID-19 cases to start with and a lower estimated treatment cost of EUR 5,600 per patient (for details see the following page).
| REVENUE MODEL | UNITED STATES - NRX TERRITORY | 2020E | 2021E | 2022E | CHANGE (%) | TOTAL NUMBER OF PATIENTS TREATED | NUMBER OF SEVERE PATIENTS TREATED | PATIENTS WITH LUNG IMPAIRMENT IN RECOVERY PHASE (%) | SYMPTOMATIC COVID-19 PATIENTS (%) | COVID-19 CASES (MN) | UNITED STATES - NRX TERRITORY | PATHWAY | 2020E | 2021E | 2022E | CHANGE (%) |
|---------------|-------------------------------|-------|-------|-------|------------|-------------------------------|---------------------------------|---------------------------------|---------------------------------|-------------------------------|-------------------------------|---------------------------------|------------|-------|-------|-------|------------|
| COSTS (CHF MN) | 20.2 | 19.2 | 18.1 | 17.1 | -5% | 20% | 40% | 32% | 25% | 10% | 10% | 10% | 10% | 10% | 10% | 10% | 10% | -4% |
| COSTS (CHF MN) | 19.2 | 18.1 | 17.1 | 16.1 | -6% | 20% | 40% | 32% | 25% | 10% | 10% | 10% | 10% | 10% | 10% | 10% | 10% | -5% |
| COSTS (CHF MN) | 18.1 | 17.1 | 16.1 | 15.1 | -7% | 20% | 40% | 32% | 25% | 10% | 10% | 10% | 10% | 10% | 10% | 10% | 10% | -6% |
| COSTS (CHF MN) | 17.1 | 16.1 | 15.1 | 14.1 | -8% | 20% | 40% | 32% | 25% | 10% | 10% | 10% | 10% | 10% | 10% | 10% | 10% | -7% |
| COSTS (CHF MN) | 16.1 | 15.1 | 14.1 | 13.1 | -9% | 20% | 40% | 32% | 25% | 10% | 10% | 10% | 10% | 10% | 10% | 10% | 10% | -8% |
| COSTS (CHF MN) | 15.1 | 14.1 | 13.1 | 12.1 | -10% | 20% | 40% | 32% | 25% | 10% | 10% | 10% | 10% | 10% | 10% | 10% | 10% | -9% |
| GDP (CHF MN) | 20.2 | 19.2 | 18.1 | 17.1 | -5% | 20% | 40% | 32% | 25% | 10% | 10% | 10% | 10% | 10% | 10% | 10% | 10% | -4% |
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| GDP (CHF MN) | 16.1 | 15.1 | 14.1 | 13.1 | -9% | 20% | 40% | 32% | 25% | 10% | 10% | 10% | 10% | 10% | 10% | 10% | 10% | -8% |
| GDP (CHF MN) | 15.1 | 14.1 | 13.1 | 12.1 | -10% | 20% | 40% | 32% | 25% | 10% | 10% | 10% | 10% | 10% | 10% | 10% | 10% | -9% |

**Notes:**
- **GDP** refers to Gross Domestic Product.
- **R&D** costs refer to Research and Development expenses.
- **NBD** costs refer to Non-Breakdown costs.
- **PROFIT** before tax refers to earnings before income tax.
- **REVENUE** refers to total revenue generated.
- **GROSS PROFIT** refers to revenue minus cost of goods sold.
- **NET PROFIT** refers to revenue minus all costs and expenses.
- **ROA** (Return on Assets) is calculated as (Net Profit / Total Assets).
- **ROE** (Return on Equity) is calculated as (Net Profit / Total Equity).
- **EPS** (Earnings Per Share) is calculated as (Net Profit / Number of Shares).
ALI and ARDS, a high unmet medical need with no approved treatments
Acute lung injury (ALI), including the most severe form known as acute respiratory distress syndrome (ARDS) or non-COVID-19 related ARDS, is a life-threatening condition in which the capacity of the lungs to oxygenate is greatly reduced even if oxygen is administered in high concentrations for instance through mechanical ventilation. Non-COVID-19 related ARDS is typically caused by blood infections (most common cause), lung infections, trauma to other parts of the body, severe burns or inhaling high concentrations of smoke and toxins. Up to 50% of these patients die despite intensive care and mechanical ventilation. There are no specific drugs approved for non-COVID-19 related ARDS.

Small phase I trial established POC in non-COVID-19 related ARDS triggers development in COVID-19
In a small phase I trial conducted in 2005, 8 patients with severe non-COVID-19 related ARDS on mechanical ventilation were treated with ascending doses of aviptadil (RLF-100 IV). Seven of the 8 patients were successfully extubated and were alive at the five day time point. Six left the hospital and one died of an unrelated cardiac event. Aviptadil has been used on a compounded basis in certain ICUs for many years in the belief that it preserves life and restores function in pulmonary hypertension, non-COVID-19 related ARDS, and acute lung injury. These promising early results in non-COVID-19 related ARDS triggered Relief’s decision in early 2020 to reposition RLF-100 IV to treat COVID-19 respiratory complications, including COVID-19 induced ARDS and prevention of COVID-19 related ARDS, with the highest priority.

Phase IIb/III ARDS trial expected to start in 2022
Following the start of the RLF-100 INHALED prevention COVID-19 related ARDS clinical trials, Relief plans to start a phase IIb/III trial of RLF-100 IV in non-COVID-19 related ARDS likely in 2022. Trial size and design have yet to be determined. Assuming RLF-100 IV is approved for COVID-19 induced ARDS, Relief plans to submit a supplemental New Drug Application (sNDA) in the US. An sNDA is an application to allow a company to make changes to the label of a product that is already the basis of an approved NDA. The FDA’s Center for Drug Evaluation and Research (CDER) must approve all important NDA changes (in packaging or ingredients, for instance) to ensure the conditions originally set for the product are still met. This would expedite US approval for RLF-100 IV in non-COVID-19 related ARDS, which could happen as early as late 2022 with launch to occur in 2023. In the EU, we expect RLF-100 IV to receive accelerated approval in 2023, given the high unmet medical need and lack of approved drugs for ARDS followed by a launch in 2024.

Orphan drug exclusivity in Europe not expected to stop generics from 2026
ALI and non-COVID-19 related ARDS are considered orphan drug indications in the EU US. Based on the positive phase I trial in non-COVID-19 related ARDS, RLF-100 IV was granted ODD in the US (2001) and EU (2007), which could provide market exclusivity of 7 years (US) or 10 years (EU) from day of first approval. Assuming approval of RLF-100 IV in COVID-19 induced ARDS in end 2022, orphan drug market exclusivity in the US would reach until end 2029 and until Q2 2032 in the EU, theoretically. However, we do not expect RLF-100 IV in COVID-19 induced ARDS to qualify as an orphan drug as the number of patients is too high. In the US, the formulation patent and expected 5 years of Hatch Waxman extension prevents the launch of generic versions of RLF-100 IV until 2034. In the
EU, the formulation patent provides protection only until 2026. Without orphan drug exclusivity for COVID-19 induced ARDS, generic versions of RLF-100 IV to treat COVID-19 induced ARDS are likely to enter the market after the formulation patent expires in 2026. Officially, they may not be promoted for use in non-COVID-19 related ARDS, but large scale generic substitution should be expected due to the price difference. Consequently, in the EU we conservatively expect protection from generics only until the formulation patent expires in 2026.

Global peak sales of CHF 450+ mn to be reached in 2026
In the US, the number of non-COVID-19 related ARDS patients is estimated at 250,000 each year of which 40% are hospitalized and an estimated 80% are eligible for treatment with RLF-100 IV. We assume US launch in early 2023 based on a successful sNDA filing. With no treatment available for non-COVID-19 related ARDS, we expect a steep uptake with the peak penetration reaching up to 50%. Assuming a treatment cost of USD 9,000 per patient, US peak sales are forecasted to amount to more than CHF 400 mn in 2033, a year before the 5 years of Hatch Waxman patent extension expires in 2034.

In the EU, we expect first launches to occur in 2024 based on successful accelerated approval. We expect a steep uptake with market penetration peaking at 30% in 2025, a year before the EU formulation patent expires. Assuming a treatment cost of EUR 4,000 per patient, EU peak sales of RLF-100 IV in non-COVID-19 related ARDS are expected to amount to approximately CHF 160 mn in 2026 (for details see the following page).
## RLF-100 IV - FINANCIAL FORECASTS FOR NON-COVID-19 RELATED ARDS

### Indication
- **Reduction of morbidity and mortality in patients with non-cOVID-19 related acute respiratory distress syndrome (ARDS)**

### Disease
- One or more escalating doses from 0.5 to 10 mg/kg intravenous administration over 2 hours followed by a course of a week.

### Price
- Cost treatment course per patient: US: $7,200; EUR 6,400 similar to COVID-19 induced ARDS treatment cost

### Standard of Care
- Personalized lung-protective mechanical ventilation combined with steroids such as dexamethasone

### Unique Selling Point
- Potentially first treatment to reduce morbidity and mortality in patients with non-cOVID-19 related ARDS

### 7% Analysis

#### Sensitivity Analysis

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</table>

### Phase 1
- **US:** Patent Expire 2029; 5-7 Year Hatch-Waxman Extension; 5 years NCE exclusivity
- **EU:** Patent expire 2026; ODD ARDS (COVID-19 ARDS Not Orphan)

### Market Penetration
- **EU:** ODD ARDS (COVID-19 ARDS Not Orphan)

### Neurocom Commercializes in US, Canada, Israel; Relief in Europe & ROW

### Profit Split (50/50)
- **Profit before tax (CHF MN) - booked by relief**

### Sales (CHF MN) - NRX Books Sales

### Summary

- **WACC (%)**
- **NPV Total Profit (CHF MN)**
- **NPV per Share (CHF MN)**

### Risk Adjusted NPV per Share (CHF)

### Sensitivity Analysis

<table>
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<tr>
<th>Variable</th>
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<th>2022E</th>
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</tbody>
</table>

### Estimates

- **Success Probability:** 35% + POC Established

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**Page 47 of 71**

**Please see important research disclosures at the end of this document**

**VALUATIONLAB | info@valuationlab.com | Valuation Report | November 2021**
RLF-100 INHALED (Pulmonary Sarcoidosis)

RLF-100 INHALED pulmonary sarcoidosis - Peak sales CHF 550+ mn; rNPV CHF 0.049/share
We forecast peak sales of CHF 556 mn for RLF-100 INHALED in pulmonary sarcoidosis in the US and EU. Relief is expected to start a phase Ib dose ranging trial in 2022 and believes first launches could occur in the US and EU in 2025 assuming fast track review, sNDA in the US and accelerated approval in the EU. We assume patent protection until 2034 in the US and patent protection in the EU until 2026 (we conservatively do not assume 10 years orphan drug exclusivity for sarcoidosis as generic versions of inhaled RLF-100 are likely to be approved for prevention COVID-19 related ARDS after formulation patent expiry in 2026) We assume an annual treatment cost per patient of USD 60,000 (US) and EUR 30,000 (EU) and peak penetration rates rising to ~8% (US) and ~3% (EU). Accounting for R&D costs (CHF ~17 mn), COGS, M&S costs (CHF ~20 mn) and the NRx profit split agreement, our rNPV amounts to CHF 217 mn or CHF 0.049 per share with a 35% (POC established) success rate and a WACC of 7% (for details see page 50).

Last but not least – Pulmonary sarcoidosis
Development of RLF-100 INHALED in pulmonary sarcoidosis was Relief’s main priority until the rapid onset of the COVID-19 pandemic in early 2020 and critical COVID-19 associated respiratory indications with high unmet need became first priority. Pulmonary sarcoidosis is a rare inflammatory disease that primarily affects the lungs but can affect almost all organs. Glucocorticoids, such as oral or inhaled prednisone, are first line treatments, while immunosuppressants such as methotrexate are given to severe patients or if glucocorticoids are ineffective or not tolerated. Chronic treatment with glucocorticoids and/or immunosuppressants is not recommended due to severe negative side effects and complications. In an early phase II trial, RLF-100 INHALED established proof-of-concept with a good effect on dry cough and shortness of breath (dyspnea) with a very good safety profile. Given the small number of patients, pulmonary sarcoidosis is qualified as an orphan disease in the US and EU. RLF-100 INHALED was granted Orphan Drug Designation in the EU (2007), providing up to 10 years market exclusivity from the date of approval. We believe pulmonary sarcoidosis is a large untapped market with a market potential amounting to approximately USD 1.7 bn for new effective, safe and well tolerated drugs, which can be given chronically. We forecast peak sales of roughly CHF 550+ mn for RLF-100 INHALED in pulmonary sarcoidosis.

RLF-100 specifically designed to be inhaled to reduce systemic side effects
Sarcoidosis is a chronic disease of unknown cause that affects many organs and tissues, most commonly the lungs. Saroidosis is characterized by specific microscopic lesions called granulomas. In general, two thirds of cases resolve spontaneously and one third of cases are long-term. In a minority of patients the disease can be life threatening. RLF-100 INHALED may provide significant benefit over current treatments including corticosteroids such as oral or inhaled prednisone or immunosuppressants such as methotrexate. Targeting the underlying pathophysiology of sarcoidosis, which manifests in dry cough, dyspnea, and fatigue, would be a clinically meaningful achievement, since it would avoid unnecessary glucocorticoid therapy with its detrimental side effects. RLF-100 INHALED’s method of action in sarcoidosis is related to its ability to influence the immune system, which may decrease the inflammatory processes seen in sarcoidosis by acting on white blood cells (lymphocytes and monocytes) involved in the formation of the granulomas. To avoid the side
effects observed with systemic delivery of VIP, and to increase the dose to therapeutically meaningful levels for pulmonary sarcoidosis, RLF-100 INHALED was specifically designed to be administered through inhalation with a nebulizer. Inhaled drugs act quickly, minimize undesired negative side effects, avoid the hepatic first-pass metabolism and act locally in the affected organ. As the size variability among adult lungs is smaller than the overall body size variability, dosing reliability is also improved when inhaling.

**RLF-100 INHALED targeted for chronic use in pulmonary sarcoidosis on positive POC**

A small phase II POC trial dubbed “AVISARCO” conducted in Germany in 20 sarcoidosis patients with RLF-100 INHALED demonstrated a noticeable effect on sarcoid inflammation, dry cough, dyspnea and quality of life. RLF-100 INHALED is currently the only known drug in development for pulmonary sarcoidosis that could potentially suppress clinical symptoms of sarcoidosis with no significant side effects. Based on these encouraging POC results, Relief plans to position RLF-100 INHALED as a first-in-class drug for chronic pulmonary sarcoidosis prescribed by specialists.

**Phase IIb dose ranging trial in pulmonary sarcoidosis expected to start in 2022**

Initially, Relief wanted to start a randomized, multicenter, double blind, placebo controlled, phase III trial named “AVISARCO II” in 200 sarcoidosis patients with a treatment duration of 24 weeks, followed by a long-term follow up of an additional 24 weeks. However, with RLF-100 INHALED likely to be approved earlier in prevention of COVID-19 related ARDS, the company has changed its clinical development plans anticipating the potential for a sNDA (supplemental New Drug Application) in the US and accelerated approval in the EU. Relief now expects to start a phase IIb dose ranging trial of RLF-100 INHALED in patients with pulmonary sarcoidosis in 2022. The company expects first launches in 2025.

**Global peak sales of CHF 550+ mn in pulmonary sarcoidosis**

We have based our detailed bottom-up forecasts for RLF-100 INHALED in pulmonary sarcoidosis largely on detailed data available in the US and extrapolated the data where possible to other regions, where detailed data is often lacking or not publicly available. We have based our estimates on sources such as the NIH, NCBI, CDC, EMA, WHO, ERS, ATS, clinicaltrials.gov and Evaluate Pharma, among others.

**Approximately CHF 550 mn peak sales in the US with first launches in 2025**

In the US, there are an estimated 25,000 newly diagnosed cases of sarcoidosis in the US each year. In a given year, approximately 185,000 patients with sarcoidosis seek medical care. The large majority of sarcoidosis patients, approximately 90%, suffer from pulmonary sarcoidosis of which an estimated 30% have chronic or advanced disease. We assume an annual treatment cost of USD 60,000 per patient, a peak penetration rate of ~8%, and patient compliance of 60% to be expected for a chronic treatment. Assuming launch in 2025 and patent protection until 2034, we forecast US peak sales of CHF 548 mn in 2033.

**Roughly CHF 30 mn peak sales in the EU with first launches in 2025**

Our EU forecasts are based on the same patient breakdown as in the US, albeit with a higher patient population. We assume a lower annual treatment cost of EUR 30,000 per patient and first launches to occur in 2025 with patent expiry in 2026. We conservatively do not assume 10 years EU orphan drug exclusivity for sarcoidosis as generic versions of inhaled RLF-100 are likely to be approved for prevention COVID-19 related ARDS after formulation patent expiry in 2026. Consequently, our peak EU peak sales amount to a modest CHF 33 mn (for details see following page).
## Valuation Report

**TREATMENT OF PULMONARY SARCOIDOSIS**

**DOSE**

**150 mg**

**PRICE**

Annual treatment cost per patient: US$ 63,000; EU: EUR 30,000

**STANDARD OF CARE**

Glucocorticoids such as prednisone or antiinflammatory drugs such as methotrexate (steroid-sparing agent)

**UNIQUE SELLING POINT**

Potentially first effective and safe treatment for patients with Pulmonary Sarcoidosis

### 7Ps Analysis

**P**ATIENT

US: Patient expires in 2021 with 5-year hatch window extension up to 2026. EU: Patient expires 2026. CDD provides 10 years exclusivity. (Not off patent)

**PATHWAY**

Phase IIIb dose-ranging trial: Start late 2021. Results Phase IIIb trial 2022. Phase IIIb trial: Approval & launch Q4 2023

**S**TATEMENT OF **C**ARE

ACCELERATED APPROVAL IN THE US AND BASED ON A SINGLE PHASE IIb/IIIa TRAIL LIKELY, POTENTIAL FOR A COMBINATORIAL 2ND PHASE III TRIAL POSSIBLE

**P**HYSICIAN

Improved quality of life and less complications and hospitalization than with current standard of care.

**P**AYER

Significantly reduces overall treatment costs with less complications and less money spent in hospital.

### REVENUE MODEL

**EU: Australia Territory**

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### SENSITIVITY ANALYSIS

**WACC (%)**

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**SUCCESS PROBABILITY**

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**ESTIMATES AS OF 30 NOVEMBER 2021**

**SOURCE**: VALUATIONLAB ESTIMATES

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*Please see important research disclosures at the end of this document.*
ACER-001 (Urea Cycle Disorders & Maple Syrup Urine Disease)

I) ACER-001 UCDs - Peak sales CHF 130+ mn; rNPV CHF 0.043/share
We forecast peak sales in the US and EU of approximately CHF 130+ mn for ACER-001 in urea cycle disorders (UCDs) assuming first launches in 2022 by Acer (US, Canada, Brazil, Turkey and Japan and Relief (EU, ROW). We calculate a rNPV of CHF 190 mn or CHF 0.043 per share assuming an 80% (Section 505(b)(2)) success rate and accounting for the 60% net profit split Relief is entitled to from Acer territories and 15% net royalties Acer is entitled to from Relief territories next to regulatory milestone payments up to USD 6 mn and up to USD 20 mn in US development and commercial launch costs (for details see page 56).

II) ACER-001 MSUD - Peak sales CHF 80+ mn; rNPV CHF 0.015/share
For ACER-001 in maple syrup urine disease (MSUD), we forecast peak sales in the US and EU to reach CHF 80+ mn assuming US launch in 2023 followed by EU launch in 2024. We calculate a rNPV of CHF 64 mn or CHF 0.015/share assuming a 35% (POC established) success rate and accounting for the same terms as for UCDs stated above (for details see page 58).

ACER-001 - new pipeline drug targeting lucrative rare diseases
In late January 2021, Relief and Acer Therapeutics signed and option agreement for exclusivity to negotiate a collaboration and license agreement for the worldwide development and commercialization of ACER-001 for the treatment of Urea Cycle Disorders (UCDs) and Maple Syrup Urine Disease (MSUD). The definitive agreement was reached in March 2021, effectively adding a new attractive, late stage, low risk, high priced, high margin rare disease compound with ACER-001 to Relief’s pipeline. Until recently Relief’s pipeline only consisted of RLF-100 in various lucrative respiratory indications, including COVID-19 complications. We conservatively forecast peak sales for both rare disease indications for ACER-001 to amount to more than CHF 200 mn based on conservative pricing assumptions with first launches in UCDs to occur in 2022. These are ultra-niche markets and accordingly will not require substantial sales forces to penetrate. Prescribers and patients alike are very concentrated with detailed registries. Therefore, these sales ought to be highly accretive for Relief. Importantly, ACER-001 in UCDs is developed under Section 505(b)(2) providing an alternative pathway for filing an NDA with a high 80% success rate and entitled to 3-years Hatch-Waxman market exclusivity from the approval date. A 5 June 2022 PDUFA date was set by the FDA when it expects to complete its review of ACER-001 in UCDs. Additionally, the FDA granted Orphan Drug Designation for ACER-001 in MSUD providing 7 years market exclusivity from the approval date. Given the low number of patients with OCDs and MSUP in the EU, we believe Relief can successfully apply for ODD in the EU resulting in 10 years market exclusivity from the approval date. The recently granted US formulation patent with taste-masking claims for ACER-001 extends protection up to 2036.

Attractive terms which can be financed through current cash or GEM SSR
Under the terms of the agreement, Acer received a USD 1 mn non-refundable payment for exclusivity until 30 June 2021 (for the initial option agreement signed in January 2021) and an additional USD 10 mn in cash and will retain development and commercialization rights in the US, Canada, Brazil, Turkey and Japan, with a 60% profit split in favor of Relief. Acer will receive 15% net sales royalties from Relief for sales in its territories (Europe, ROW) and

Please see important research disclosures at the end of this document
a total of up to USD 6 mn milestones based on the first EU marketing approvals of ACER-001 in UCDs and MSUD. Relief will pay up to USD 20 mn in US development and commercial launch costs for the UCDs and MSUD indications, of which USD 15 mn has been paid to-date. Relief can fund the ACER-001 agreement out of its current cash position, from potential first commercial sales of RLF IV in COVID-19 induced ARDS or ultimately through the recently announced CHF 50 mn Share Subscription Facility (SSF) with largest shareholder GEM.

I) ACER-001 UCDs - Peak sales CHF 130+ mn; rNPV CHF 0.043/share

ACER-001 has an attractive profile in UCDs providing a lucrative switch opportunity

UCDs are a rare group of disorders caused by genetic mutations that result in a deficiency in one of the six enzymes that catalyze the urea cycle, which can lead to an excess accumulation of ammonia in the bloodstream, a condition known as hyperammonemia. Acute hyperammonemia can cause lethargy, somnolence, coma, and multi-organ failure, while chronic hyperammonemia can lead to headaches, confusion, lethargy, failure to thrive, behavioral changes, and learning and cognitive deficits. Common symptoms of both acute and chronic hyperammonemia also include seizures and psychiatric symptoms. UCDs is an ultra-rare orphan disease with the incidence estimated to be at least 1:35,000 births. Partial defects of the urea cycle make the number much higher. UCDs are estimated to affect less than 10,000 patients in the US and a slightly higher number of patients in the EU based on the size of the EU population. The current treatment of UCDs consists of dietary management to limit ammonia production in conjunction with medications that provide alternative pathways for the removal of ammonia from the bloodstream. Some patients may also require individual branched-chain amino acid supplementation.

Taste-masking a first USP with the potential to improve patient compliance

Current drugs such as Horizon Therapeutics’ Buphenyl (glycerol phenylbutyrate) and Ravicti (sodium phenylbutyrate) are effective treatments in managing ammonia levels. However, they are pricy, must be taken frequently with food and include unpleasant taste, leading to patient non-compliance. ACER-001 is a taste-masked, immediate-release (IR) proprietary powder formulation of sodium phenylbutyrate (NaPB) developed by Acer using a microencapsulation process. ACER-001 microparticles consist of a core center, a layer of active drug, and a taste-masking coating which dissolves in the stomach, allowing taste to be neutralized while still allowing for rapid systemic release. If ACER-001 is approved in UCDs, its taste-masked properties could make it a compelling alternative to existing NaPB-based treatments, such as Horizon’s Buphenyl and Ravicti as the unpleasant taste associated with NaPB is cited as a major impediment to patient compliance with those treatments. In 2019, sales of Buphenyl and Ravicti amounted to USD 239 mn, up 19% yoy. Note that in March 2015, Horizon Pharma acquired Hyperion Therapeutics for approximately USD 1.1 bn in cash to expand and diversify its orphan drug product portfolio with Buphenyl and Ravicti.

Compelling data showing bioequivalence to Buphenyl…

In July 2020, Acer announced data from a food effect study in healthy volunteers showing that administration of ACER-001 in a fasted state increased systemic exposure of phenylbutyrate (PBA), phenylacetate (PAA) and phenylacetylglutamine (PAGN) levels compared to fed state, and therefore based on modeling data may improve disease management in patients with UCDs when compared to currently approved treatments requiring administration with food.
Results from Part B of the ACER-001 bioequivalence (BE) trial in healthy volunteers (n=36), announced in February 2020, showed that ACER-001 was bioequivalent to Buphenyl and were within the parameters recommended by the FDA’s Guidance for Industry, “Statistical Approaches to Establishing Bioequivalence.” The BE trial included a food effect study, which evaluated the pharmacokinetics (PK) of sodium phenylbutyrate (NaPBA) showing that administration of ACER-001 in a fasted state achieved more than two times the maximum concentration (Cmax) of PBA compared to administration of the same dose of ACER-001 in a fed state. These results are consistent with previously published data by Nakano, et al. that evaluated PK of NaPBA in patients with progressive familial intrahepatic cholestasis, also demonstrating that administration of NaPBA in a fasted state significantly increased PBA peak plasma concentration compared to administration of NaPBA in a fed state.

…and the potential of ACER-001 to be given without food, another USP
Currently approved therapies for UCDs, including Buphenyl and Ravicti are required to be administered with food. Buphenyl is required to be administered in a fed state due to its aversive odor and taste, with side effects including nausea, vomiting and headaches, which often lead to discontinuation of treatment. Additionally, prescribing information states that Buphenyl food effect is unknown. Ravicti PK and pharmacodynamic (PD) properties were determined to be indistinguishable in fed or fasted states. ACER-001 is uniquely formulated with its multi-particulate, taste-masked coating to allow for administration in a fasted state, while still allowing for rapid systemic release.

Based on the results from the food effect study within the ACER-001 BE trial, Acer commissioned Rosa & Co. LLC to create a PhysioPD PK model to evaluate the potential food effect on exposure, tolerability and efficacy of ACER-001 in UCDs patients. Results from this in silico model suggest that administration of ACER-001 in a fasted state required approximately 30% less PBA to achieve comparable therapeutic benefit in a fed state. In addition, the model predicted that administration of ACER-001 in a fasted state compared to administration of Buphenyl or Ravicti (same amounts of PBA) in their required fed states is expected to result in higher peak blood PBA, PAA and PAGN concentrations, predicting a 43% increase in urinary PAGN levels (a negative correlation between blood ammonia area under the curve and 24-hour urinary PAGN amount has been demonstrated). The results of the ACER-001 food effect study, published literature and in silico modeling suggest that ACER-001 administered in a fasted state, and likely just 10 minutes prior to meals, could offer UCD patients a safe and better disease management option compared to currently approved products that are required to be taken with food.

ACER-001 developed under Section 505(b)(2) provides 3 years market exclusivity
Acer is developing ACER-001 under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, which provides a potentially streamlined path for companies that have developed improvements to drug products previously approved by the FDA. Section 505(b)(2) provides an alternative pathway for submission of an NDA, referred to as a 505(b)(2) application, when some or all of the safety and efficacy investigations relied on for approval were not conducted by or for the applicant and for which the applicant has not obtained a right of reference but for which the relevant information is publicly available. The Hatch-Waxman Amendments also provide pharmaceutical products approved under Section 505(b)(2) with potential market exclusivity for three years from FDA approval. Moreover, after the successful BE trials, ACER-001 is highly likely to be approved by the FDA, which justifies an 80% success rate, in our view.
Several gene approaches stumble, are years away with prohibitive pricing
We do not expect gene therapy approaches - even if they prove highly effective clinically - to prevent achievement of market traction with ACER-001, since these will inevitably need to be priced at USD 500,000 to USD 1,000,000 or more per patient (since they are one-time treatments) and accordingly shall only address a small segment of the overall market. Ultragenyx’ DTX301 is the most advanced gene therapy for curative approaches to ornithine transcarbamylase (OTC) deficiency, the most common urea cycle disorder with phase II/Il ongoing. Translate Bio’s MRT5201 is on clinical hold, while CureVac handed rights to Arcturus Therapeutics in 2019.

Successful US NDA filing with a 5 June 2022 PDUFA data set by the FDA
In May 2021, Relief’s partner Acer announced a positive outcome from a pre-NDA (New Drug Application) meeting with the FDA to discuss the content of Acer’s planned NDA submission of ACER-001 for the treatment of patients with UCDs (urea cycle disorders). Based on FDA feedback, the proposed data package is deemed to be sufficient to support an NDA submission under Section 505(b)(2) regulatory pathway for this indication. In August 2021, Acer filed an NDA under Section 505(B)(2) regulatory pathway for US approval of ACER-001 in urea cycle disorders (UCDs) and shortly after received acceptance of filing triggering the FDA review with a 5 June 2022 Prescription Drug User Fee Act (PDUFA) date when the FDA is expected to complete its review.

CHF 130+ mn peak sales in UCDs with first launches in 2022
We have based our detailed bottom-up forecasts for ACER-001 largely on detailed data available in the US and extrapolated the data where possible to other regions, where detailed data is often lacking or not publicly available. We have based our estimates on sources such as NORD, GARD, NIH, HHS, and Acer Therapeutics, among others.

To account for regional differences, we provide detailed forecasts for the US and Europe. Sales in regions such as Canada, Brazil, Turkey, Japan and Asia could provide substantial upside to our forecasts. We conservatively forecast until 7 years orphan drug exclusivity expiry in the US in 2029 and 2032 in the EU (assuming ODD due to the low number of patients in EU). The recently issued US formulation patent covering the taste-masking claims now extend protection up to 2036. The Hatch-Waxman Amendments under Section 505(b)(2) provide ACER-001 with potential market exclusivity for three years from FDA approval.

Based on estimated incidence figures of individual UCDs (CPS1, OTC, ASS1, ASL, ARG1, ornithine translocase and citrin deficiencies) from Ah New N et al. “Urea Cycle Disorders Overview”, we estimate there are approximately 9,500 UCDs patients in the US We assume ~80% of these patients have been diagnosed and that ~90% are eligible for ACER-001 treatment. In the US, we conservatively assume an annual treatment cost of USD 120,000 per patient with a 90% patient compliance due to the improved formulation with taste-masking and the potential to take ACER-001 without food. Assuming launch in 2022 and peak market penetration conservatively reaching to ~12%, we forecast US peak sales of CHF 107 mn in 2028.

Applying a similar approach to the EU with an annual treatment cost of USD 60,000, launch in 2022 and a conservative peak market penetration of ~8%, we forecast CHF 47 mn peak sales for the EU in 2030 (for details see page 56).
Sales forecasts may prove conservative and will be highly accretive for Relief

Note that these peak sales forecasts are conservative and expected to be highly accretive for Relief. For instance, our pricing assumptions are decidedly conservative when compared to current Buphenyl (USD 200k-400k) and Ravicti (USD 200k-1.2 mn) pricing and the prices of other ultra-orphan small molecule drugs, potentially resulting in higher market penetration than forecast. We have not captured sales outside the US and EU, which could be meaningful. Some of these markets such as Brazil would be addressable once and FDA approval has been secured. Prescribers and patients alike are very concentrated with detailed registries and can be covered by a sales force of ~10 people in the US and 15-20 in the EU. Relief might use a contract commercial organization (CCO) with substantial experience in selling ultra-orphan drugs. The API of ACER-001 has been well-known for an extended period and is relatively inexpensive to manufacture.
### Sensitivity Analysis

**WACC (%)**

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<th>CHF SHARE</th>
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**SUCCESS PROBABILITY**

- 80%: 0.048, 0.046, 0.044, 0.042, 0.040, 0.038, 0.036, 0.034, 0.032
- 75%: 0.045, 0.043, 0.041, 0.039, 0.037, 0.035, 0.033, 0.031, 0.029
- 70%: 0.051, 0.049, 0.047, 0.045, 0.043, 0.041, 0.039, 0.037, 0.035

**RISK ADJUSTED NPV PER SHARE (CHF)** 0.043

**Source:** VALUATIONLAB ESTIMATES

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**ACER-001 - FINANCIALS FOR UREA CYCLE DISORDERS (UCDS)**

**INDICATION:** Treatment of hyperammonemia (accumulation of ammonia) in patients with urea cycle disorders (UCD).

**DOSE:** TBD

**PRICE:** Annual treatment cost per patient: US$ 120,000. Euro: US$ 60,000

**STANDARD OF CARE:** Horizon therapies' Buprenyl and Invicyst.

**Sensitivity Rounding:** Potentially first form of sodium phenylbutyrate that can be taken without food with unique taste-masking formulation at a competitive price.

**7Ps Analysis**

- **PATIENT:** Issued US formulation (taste-masked) patent expires 2030; CRP (human drug designation exclusion) in the US (7 years) and EU (10 years) from approval date.
- **PHASE:** Under section 109(b) ACER-001 has proven bioequivalence to Buprenyl, with a high likelihood to be approved. Justifying a 80% success rate.
- **PATHWAY:** Developed under section 505(b)(2) for improvements to products previously approved by the FDA.
- **PATIENT:** Higher patient compliance due to the taste-masked formulation and first form of sodium phenylbutyrate that can be given without food.

**Revenue Model**

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<th>Year</th>
<th>2020E</th>
<th>2021E</th>
<th>2022E</th>
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<th>2024E</th>
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<td>13,234</td>
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<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
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<tr>
<td><strong>UCD Patients Diagnosed (%)</strong></td>
<td>80%</td>
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<td><strong>UCD Patients Diagnosed</strong></td>
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<td><strong>Patient Compliance (%)</strong></td>
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<td><strong>Sales (CHF MN): ACER Therapeutics Books Sales</strong></td>
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Please see important research disclosures at the end of this document.
II) ACER-001 MSUD - Peak sales CHF 80+ mn; rNPV CHF 0.015/share

MSUD – treating an ultra-rare disease with no available drug treatments
Maple syrup urine disease (MSUD) is a rare but serious inherited condition whereby the human body cannot process certain amino acids (the “building blocks” of protein), causing a harmful build-up of substances in the blood and urine. The human body breaks down protein foods such as meat and fish into amino acids. Any amino acids that are not needed are usually broken down and removed from the body. Infants with MSUD are unable to break down the amino acids leucine, isoleucine and valine. Very high levels of these amino acids are harmful. Without treatment, severe, life-threatening symptoms can develop, including seizures (fits) or falling into a coma. Some children with untreated MSUD are also at risk of brain damage and developmental delay. One of the characteristic symptoms of MSUD is sweet-smelling urine, which gives the condition its name. Other than a highly restricted diet of branched-chain amino acid (BCCA) free synthetic foods and formula, there are no currently approved treatments for MSUD.

POC of treatment with NaPB (active ingredient ACER001) established in MSUD
Therapy with sodium phenylacetate/benzoate or sodium phenylbutyrate (NaPB) in UCDs patients has been associated with a selective reduction in branched-chain amino acids (BCAA) in spite of adequate dietary protein intake. Based on this clinical observation, the potential of phenylbutyrate treatment to lower BCAA and their corresponding a-keto acids (BCKA) in patients with classic and variant late-onset forms of maple syrup urine disease (MSUD) was investigated. In vitro and in vivo experiments to elucidate the mechanism for this effect were also performed. BCAA and BCKA are both significantly reduced following phenylbutyrate therapy in control subjects and in patients with late-onset, intermediate MSUD. In vitro treatment with phenylbutyrate of control fibroblasts and lymphoblasts resulted in an increase in the residual enzyme activity, while treatment of MSUD cells resulted in the variable response which did not simply predict the biochemical response in the patients. In vivo phenylbutyrate increases the proportion of active hepatic enzyme and unphosphorylated form over the inactive phosphorylated form of the E1a subunit of the branched-chain a-keto acid dehydrogenase complex (BCKDC). Using recombinant enzymes, it was shown that phenylbutyrate prevents phosphorylation of E1a by inhibition of the BCKDC kinase to activate BCKDC overall activity, providing a molecular explanation for the effect of phenylbutyrate in a subset of MSUD patients. Therefore, phenylbutyrate treatment may be a valuable treatment for reducing the plasma levels of neurotoxic BCAA and their corresponding BCKA in a subset of MSUD patients.

Phase IIb/III trials could start in 2022 with a potential US and EU launch in 2024
Based on these encouraging POC trial results Acer and Relief plan to start phase IIb/III development of ACER-001 in MSUD in 2022 with a potential launch in the US and EU in 2024.

CHF 80+ mn peak sales in MSUD with first launches in 2024
The estimated number of patients affected with MSUD in the US is approximately 2,500 and ~3,300 in the EU. We assume 80% are not diagnosed and 90% are eligible for ACER-001 treatment. Applying the same conservative pricing as for UCDs and market penetration ranging between 25% (US) and ~30% (EU) we forecast peak sales for ACER-001 in MSUD to amount to CHF 85 mn (for details see following page).
### Valuation Model

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<tbody>
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<td>2'524</td>
<td>2'939</td>
<td>3'393</td>
<td>3'908</td>
<td>4'400</td>
<td>4'964</td>
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<td>11'630</td>
<td>12'770</td>
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<td><strong>MSUD PATIENTS DIAGNOSED (%)</strong></td>
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<tr>
<td><strong>NUMBER OF MAPLE SYRUP URINE DISEASE (MSUD) PATIENTS</strong></td>
<td>2'148</td>
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<td><strong>GROWTH (%)</strong></td>
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<td><strong>MSUD PATIENTS DIAGNOSED (%)</strong></td>
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### Sensitivity Analysis

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<tr>
<td><strong>SUCCESS PROBABILITY</strong></td>
<td>30%</td>
<td>30%</td>
<td>30%</td>
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**Estimates as of 22 November 2021**
Golike (Phenylketonuria - PKU)

I) Golike in PKU - Peak sales CHF 50+ mn; rNPV CHF 0.028/share
Global peak sales for the Golike family of food for special medical purposes (FSM) products for phenylketonuria (PKU) are guided to reach CHF 50+ mn. Golike has already been launched in Europe with the US to follow in H1 2021. Development as a prescription-only treatment in the US could boost peak sales substantially to more than CHF 200 mn. A strong growth path has been established by APR with a clear life cycle management strategy through 2024 with the rollout of additional complementary Golike products. Golike is marketed by an own direct sales team in selected European countries as well as established distribution partners. Assuming average COGS of 25%, R&D costs of 5% and M&S of 15% during the product life cycle, we calculate an NPV of CHF 123 mn or CHF 0.028 per share (for details see page 60)

Golike – A complete family of FSMP engineered products for phenylketonuria (PKU)
The recent acquisition of APR expands Relief’s pipeline further with compounds targeting rare inherited metabolic recessive disorders such as Golike for patients with phenylketonuria (PKU). Golike is the first line of food for special medical purposes (FSMP) products engineered with APR’s drug delivery Physiomimic™ Technology offering an improved metabolic management for patients with PKU and a better compliance thanks to minimized taste, odor and aftertaste. The proprietary and patented Physiomimic™ Technology is the first and only technology able to control and prolong release of multiple active ingredients (up to 19 amino acid mixes) simultaneously in the most prevalent, rare, inherited metabolic diseases. Beyond Golike, APR is developing optimized amino acid mix-based products for other rare metabolic disorders, such as tyrosinemia, homocystinuria and maple syrup urine disease (MSUD). For MSUD, such a product is expected to be highly complementary to Relief’s ACER-001, which is also in development for treatment of this disease and possesses effective taste-masking properties. Golike was approved in the EU in 2018. A direct sales and marketing team is in place in selected European countries to support Golike, as well as established distribution partnerships for other countries in Europe and beyond. US approval is expected around year-end 2021 with launch to start in H1 2022.

PKU patients must maintain a lifelong strict diet to have a normal life span
PKU is a rare inherited disorder caused by a defect of the enzyme needed to break down phenylalanine, leading to a toxic buildup of the amino acid phenylalanine (Phe) when eating foods that contain protein or aspartame that can eventually lead to serious health problems. Untreated, PKU can lead to intellectual disability, seizures, behavioral problems, and mental disorders. It may also result in a musty smell and lighter skin. A baby born to a mother who has poorly treated PKU may have heart problems, a small head, and low birth weight. PKU affects on average about 1 in 10,000 newborns in develop countries. Males and females are affected equally. Approximately 350,000 patients suffer from PKU in the world’s key markets.

Standard of care for PKU is mainly based on two essential pillars:

1. A lifelong low protein diet (that limits Phe intake from foods)
2. Protein substitute administration (to support physiological protein synthesis)

The diet should begin as soon as possible after birth and to be continued for life. Patients who are diagnosed early and maintain a strict diet can have normal health and a normal life...
span. The main objective of the treatment is to maintain Phe levels in the recommended range, and the efficacy of the treatment is strongly influenced by compliance to the prescribed diet. As seen on evidence, compliance becomes increasingly difficult with age due to diverse factors. Bad taste, odor and aftertaste of amino acid-based protein substitutes are still a big issue that generate an important number of adults out of diet. Moreover, scientific evidence indicates that significant sub-optimal health outcomes still exist in compliant PKU patients. This is mainly due to the absorption profile of free amino acids (AA), which is very different from that of intact natural proteins. Free amino acids bypass the digestive phase giving place to plasma levels of amino acids that are higher, peak faster and decrease more quickly. Thus, the diverse kinetic profile of free amino acids has an impact on body metabolism and consequently affects the health of people with PKU.

Golike’s minimized taste, odor and aftertaste offers better patient compliance

Golike is the first controlled-release amino acid mix product with effective taste and odor masking. With these characteristics, Golike is a uniquely differentiated product, offering improved metabolic management and better compliance for PKU patients of all age groups. The Golike line of products include sachets, shake and drink to be merged in a unique Ready to Drink formulation, while Golike krunch and bars will be launched soon and extended with different flavors over time.

Relief to expand APR’s European sales infrastructure and seek US approval

Following APR’s launch of Golike in Europe in 2018, Relief is planning to expand the commercial infrastructure beyond the current countries and to refine the marketing activities to increase and accelerate future growth. In other countries, Golike is available as a prescription only, fully reimbursed product for PKU. In the US, Golike has been granted Orphan Drug Designation, and Relief intends to assess options to pursue approval of Golike as a prescription product. US approval is expected by around year-end 2021 with commercial launch in H1 2022. A strong growth path has been established by APR with a clear life cycle management strategy through 2024 with the rollout of additional complementary Golike products. Global peak sales for the Golike family of FSMP products for PKU are guided to reach CHF 50+ mn. Development as a prescription-only treatment with significantly in the US could boost peak sales substantially to more than CHF 200 mn.
APR-TD011 (Epidermolysis bullosa - EB)

I) APR-TD011 in EB - Peak sales CHF 900+ mn; rNPV CHF 0.170/share
We forecast global peak sales of more than CHF 900 mn for APR-TD011 in epidermolysis bullosa (EB) with first launches to occur in 2026. In the US, APR-TD011 will enjoy at least 7-years orphan drug market exclusivity based on granted ODD. In the EU, Relief will seek ODD, which would provide 10-years market exclusivity. We assume an annual treatment price per patient of USD 70,000 in the US and EUR 40,000 in the EU with a conservative 50% peak penetration rate in eligible EB patients in both regions. We calculate a rNPV of CHF 748 mn or CHF 0.170 per share assuming an 35% (POC) success rate and accounting for COGS of 5%, R&D costs of roughly CHF 20 mn and M&S costs of ranging between CHF 15-25 mn for each region. (for details see page 63)

APR-TD011 is potentially the first effective and convenient treatment for EB
APR-TD011 is a sprayable hypochlorous acid (HClO) solution that combines strong antimicrobial activity with anti-inflammatory properties based on APR's Tehclo™ technology with the potential to become one of the first products ever approved for EB. Tehclo™ is a globally patented nano-technology platform applied to the production of a unique HClO solution that ensures the most consistent quality for best-in-class clinical outcomes. APR TD011 is designed to be a complete treatment for EB patients to prevent or reduce infections and inflammation through modulation of the wound microenvironment to support a faster physiological wound healing.

EB is a rare disease characterized by life ruining skin blistering which can be fatal
Epidermolysis bullosa (EB) is a group of rare, genetic, life-threatening connective tissue disorders characterized by easy blistering of the skin and mucous membranes throughout the body with the risk of severely impacting internal organs. Blisters occur with minor trauma or friction and are painful. Its severity can range from mild to fatal. Those with mild cases may not develop symptoms until they start to crawl or walk. Complications may include esophageal narrowing, squamous cell skin cancer, and the need for amputations. EB is caused by a mutation in at least one of 16 different genes. Some types are autosomal dominant while others are autosomal recessive. The underlying mechanism is a defect in attachment between or within the layers of the skin.

The main types of EB include:
1. **Epidermolysis bullosa simplex (EBS):** is a form of EB that causes blisters at the site of rubbing. It typically affects the hands and feet, and is typically inherited in an autosomal dominant manner, affecting the keratin genes KRT5 and KRT14. Therefore, there is a failure in keratinization, which affects the integrity and the ability of the skin to resist mechanical stresses. EBS accounts for roughly 92% of EB cases and patients tend to die in infancy.
2. **Dystrophic epidermolysis bullosa (DEB):** is an inherited variant affecting the skin and other organs. DEB is caused by genetic defects (or mutations) within the human COL7A1 gene encoding the protein type VII collagen (collagen VII). DEB-causing mutations can be either autosomal dominant or autosomal recessive. Epidermis bullosa pruriginosa and albopapuloid epidermolysis bullosa (Pasini's disease) are rare subtypes of this disease. DEB accounts for roughly 5% of EB cases and patients tend to die in early adulthood.
3. **Junctional epidermolysis bullosa (JEB):** is an inherited disease affecting laminin and collagen. This disease is characterized by blister formation within the lamina lucida of the basement membrane zone and is inherited in an autosomal recessive manner. It also presents with blisters at the site of friction, especially on the hands and feet, and has variants that can occur in children and adults. JEB accounts for roughly 1% of EB cases and patients tend to die in infancy.

The diagnosis is suspected based on symptoms and confirmed by skin biopsy or genetic testing. There is no cure for the condition. Management involves daily wound care, bandaging, pain control, controlling infections, nutritional support, and prevention and treatment of complications. There are an estimated 250,000 patients with EB worldwide, with an estimated 30,000 patients in the European Union (EU) and 20,000 patients in the US. EB occurs equally commonly in males and females.

**POC shows promising results with improvement of skin blistering in just 2 weeks**
APR-TD011 was granted Orphan Drug Designation (ODD) in late 2019 by the US FDA. In a preliminary clinical trial, EB patients administered with APR-TD011 demonstrated improvement in skin blistering and tissue repair within just two weeks of treatment and was shown to be well tolerated with a favorable safety profile. APR-TD011 has shown favorable safety and tolerability through exposure to more than 300 individuals with various types of skin wounds and lesions. Moreover, the same active ingredient in APR-TD011, the sprayable hypochlorous acid (HClO) solution, is approved as a Class III medical device under the Nexodyn brand for treating acute and chronic wounds.

**Potentially pivotal phase IIb trial to start in 2022 after discussions with regulators**
The next trial is slated to be a phase IIb dose ranging trial with the potential (depending on its scope) to be regarded as registrational in nature. In particular, when taking into account the limited size of the phase III “EASE” trial that Amryt Pharma (symbol: AMYT) did with Oleogel-S10 (Filsuvez), a topical gel, in 223 adults and children with either junctional EB, dystrophic EB, or Kindler syndrome across 28 countries. Patients with EB simplex were excluded from the trial. In June 2021, The FDA granted Priority Review (6 months instead of 10) for Oleogel-S10 with a 30 November 2021 Prescription Drug User Fee Act (PDUFA) date by when the FDA has to complete its review. Relief plans to discuss next development steps with regulatory authorities later this year, with the goal of initiating a phase II phase IIb dose ranging trial in 2022. First launches of ADR-TD011 in EB could occur in 2026. In the US, the compound will enjoy at least 7-years orphan drug exclusivity from day of approval. Relief plans to apply for ODD in the EU, which will provide at least 10-years market exclusivity from approval if granted by the EMA.

**Peak sales potential of CHF 900+ mn with first launches expected in 2026**
In the US, there are an estimated 25,000 EB patients with approximately 35,000 in the EU. We conservatively assume roughly 50% of patients are eligible for APR-TD011 treatment with an annual treatment cost per patient of USD 70,000 in the US and EUR 40,000 in the EU. Assuming first launches in 2026, 7-years US orphan drug market exclusivity, based on granted ODD in 2019, and 10-years in the EU (the EU has yet to grant ODD) from approval, global peak sales of APR-TD011 in EB could easily amount to more than CHF 900 mn in the US and the EU (for details see following page).
## APTR011 - FINANCIAL FORECASTS FOR EPIDERMOLYSIS BULLOSA (EB)

### REVENUE MODEL

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### EUROPE - RELIEF SALES FORCE

| **NUMBER OF EPIDERMOLYSIS BULLOSA (EB) PATIENTS** | 17'036 | 17'207 | 17'352 | 17'728 | 18'095 | 18'362 | 18'649 | 18'936 | 19'223 | 19'510 | 19'510 |
| **GLOBAL SALES (USD MN)** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **GLOBAL SALES (CHF MN)** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **PROFIT BEFORE TAX (CHF MN)** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

### UNITED STATES - RELIEF SALES FORCE

| **NUMBER OF EPIDERMOLYSIS BULLOSA (EB) PATIENTS** | 10'090 | 10'400 | 10'735 | 11'102 | 11'456 | 11'810 | 12'168 | 12'530 | 12'924 | 13'327 | 13'327 |
| **GLOBAL SALES (USD MN)** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **GLOBAL SALES (CHF MN)** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **PROFIT BEFORE TAX (CHF MN)** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

### GLOBAL SALES (CHF MN)

| **CHANGE (%)** | 0 | -3% | -3% | -3% | -3% | -3% | -3% | -3% | -3% | -3% | -3% |

### GLOBAL SALES (USD MN)

| **CHANGE (%)** | 0 | -3% | -3% | -3% | -3% | -3% | -3% | -3% | -3% | -3% | -3% |

### GLOBAL PROFIT (CHF MN)

| **CHANGE (%)** | 0 | -3% | -3% | -3% | -3% | -3% | -3% | -3% | -3% | -3% | -3% |

### WACC (%)

| **NPV TOTAL PROFIT (CHF MN)** | 7% | 7% | 7% | 7% | 7% | 7% | 7% | 7% | 7% | 7% | 7% |
| **NUMBER OF SHARES (MN)** | 2138 | 2138 | 2138 | 2138 | 2138 | 2138 | 2138 | 2138 | 2138 | 2138 | 2138 |

### SUCCESS PROBABILITY

35% POC ESTABLISHED IN WOUND HEALING

### RISK ADJUSTED NPV PER SHARE (CHF)

| **0.170**

### SENSITIVITY ANALYSIS

| **WACC (%)** | 5.5 | 6.0 | 6.5 | 7.0 | 7.5 | 8.0 | 8.5 |
| **NPV TOTAL PROFIT (CHF MN)** | 7% | 7% | 7% | 7% | 7% | 7% | 7% |
| **NUMBER OF SHARES (MN)** | 2138 | 2138 | 2138 | 2138 | 2138 | 2138 | 2138 |
| **SUCCESS PROBABILITY** | 35% POC ESTABLISHED IN WOUND HEALING

### ESTIMATES AS OF 30 NOVEMBER 2021

| **SOURCE: VALUATIONLAB ESTIMATES** | 2021E | 2022E | 2023E | 2024E | 2025E | 2026E | 2027E | 2028E |
| **GLOBAL SALES (USD MN)** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **GLOBAL PROFIT (CHF MN)** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

### INDICATION

TO PREVENT OR REDUCE INFECTIONS AS WELL AS INFLAMMATION IN SKIN BLISTERING AND TO IMPROVE TISSUE REPAIR IN PATIENTS WITH EPIDERMOLYSIS BULLOSA

### DOSAGE

TRIO

### PRICE

ANNUAL TREATMENT COST PER PATIENT: WE ASSUME USD 70,000 IN THE US AND EUR 40,000 IN THE EUROW

### STANDARD OF CARE

NO APPROVED TREATMENT FOR EB: SUPPORTIVE TREATMENTS SUCH AS PAIN AND WOUND MANAGEMENT TO PREVENT INFECTIONS AND SUSTAIN WOUND HEALING

### UNIQUE SELING POINT

CONVENVENT AND WELL TOLERTATED SPRAY WITH FAST REDUCTION OF SKIN BLISTERING AND IMPROVEMENT IN TISSUE REPAIR

### 7P ANALYSIS

| **PATENT** | PRIMARY PROTECTION IS MARKET EXCLUSIVITIES SUCH AS ORPHAN DRUG DESIGNATION (COGS GRANTED IN THE US IN 2019; RELIEF WILL SEEK IIN THE EU)
| **PHASE** | PHASE I COMPLETED; PHASE II CLINICAL TRIAL EXPECTED TO START IN 2022; FIRST LAUNCHES GUIDED FOR 2025
| **PATHWAY** | IN THE US CONSIDER A COMBINATION OF A MEDICAL DEVICE AND PHARMACEUTICAL REQUIRING CLINICAL TRIALS; EU REGULATORY PATHWAY TO BE DETERMINED
| **PHYSICIAN** | IMPROVED QUALITY OF LIFE THROUGH LESS SKIN BLISTERING AND PAIRED CAUSED BY INFECTIONS AND INFLAMMATION
| **PAYER** | LOWER OVERALL TREATMENT COSTS DUE TO LESS SKIN BLISTERING AND IMPROVED TISSUE REPAIR
| **PARTNER** | RELIEF EXPECTS TO SELL APTR011 THROUGH AN OWN SPECIALIST SALES FORCE IN THE KEY MARKETS INCLUDING THE US AND EU

### November 2021

Please see important research disclosures at the end of this document.
Management Team

Lean management team to rapidly expand as company evolves
Relief’s management team strategy is to maintain a lean internal structure and a series of collaborations with relevant worldwide experts. The management team works collectively to execute all duties traditionally assigned to a CEO. Relief is firstly focused on building the right team to see RLF-100 through clinical development and to expand the management team as the company evolves. In parallel, the company is setting up a team of experts to handle all commercial aspects associated with a potential approval of RLF-100 to ensure reaching patients timely.

Management biographies

Jack Weinstein (Chief Financial Officer and Treasurer)
Jack Weinstein joined Relief in October 2020 as its US based Chief Financial Officer and Treasurer. He brings over 40 years of wide-ranging executive management expertise, including as a CFO, investment banker and consultant in the biopharmaceutical and life sciences industries. Jack has extensive experience in finance and healthcare investment banking, corporate and business development as well as FDA regulatory and intellectual property strategies. He has successfully completed a variety of corporate finance transactions, including public and private financings, as well as merger and acquisition transactions. Before joining Relief, Jack served as Managing Director and Head of Healthcare Investment Banking at Avalon NetWorth, an independent New York-based boutique investment bank. Prior to Avalon, he was CFO, Treasurer and Vice President of Business Development at Catalyst Pharmaceuticals, Inc. (NASDAQ symbol: CPRX), a biopharmaceutical company developing prescription pharmaceutical products to treat orphan diseases. Jack eventually took the company public through a full-blown IPO on the Nasdaq Global Market. He also was President and Founder of The Sterlington Group, Inc. a consulting firm providing strategic, business development, regulatory and “CFO” consulting services, including M&A advisory and raising equity and debt for middle-market companies. Adding to his credentials, Jack gained experience at several other investment banking and consulting firms. He holds an MBA from Harvard University.

Taneli Jouhikainen (Chief Operating Officer)
Dr. Taneli Jouhikainen has over 25 years of life sciences expertise. He joins Relief from Savara, a Nasdaq-listed clinical stage biopharmaceutical company focused on rare respiratory diseases, where he was Co-Founder and President & COO. Prior to this, he served at Akela Pharma Inc., a public clinical stage specialty pharmaceutical company focused on orphan drugs and inhalation products, first as Head of Corporate Development and subsequently as CEO until the company’s merger with Nventa Biopharmaceuticals. He served in senior executive roles at various other life sciences companies, including LAB International, Inc. and Focus Inhalation Oy, and was Head of Clinical Development at Leiras, a subsidiary of Schering AG. Dr. Jouhikainen holds an M.D. and a Ph.D. in hematology and immunology from the University of Helsinki and an MBA from the Helsinki School of Economics.

Anthony M. Kim (Head US Commercial Operations) – per 1 December 2021
Prior to joining Relief, for the past three years, Mr. Kim was Vice President, Global Commercial Development at Novocure, where he led a 21-person team in the planning and
U.S. marketing execution for that company’s Optune® and Optune Lua™, FDA-approved, therapeutic devices that deliver alternating electrical fields to treat patients with Glioblastoma Multiforme and Mesothelioma. From 2017 to 2018, he was Executive Director of Marketing at Ignyta (subsequently acquired by Roche), during which time he led the development of the commercial launch plan for entrectinib, an oral, oncologic agent in pan-tumor clinical trials for patients with neurotrophic tyrosine receptor kinase (NTRK) and ROS1 fusion-positive disease. From 2012 to 2017, Mr. Kim held positions of increasing responsibility at Alexion Pharmaceuticals, Inc., most recently serving as Director, Head of U.S. Marketing, Hypophosphatasia, where he managed the U.S. marketing efforts for the launch of Strensiq, a novel, first-in-class enzyme replacement therapy for the treatment of hypophosphatasia, a rare inherited metabolic bone disorder. Earlier, from 2004 to 2012, Mr. Kim held various positions at Genentech, including Product Manager, Herceptin Marketing and Divisional Sales Manager, Rituxan Hematology. Mr. Kim received his Bachelor of Arts Degree from Harvard University and a Master of Business Administration from The Wharton School.

Paolo Galfetti (President of Relief Europe)
Paolo Galfetti is the CEO of APR Applied Pharma Research S.A. He has over twenty years of management experience in the pharmaceutical sector, including in the areas of business development and licensing, operational strategic management, clinical research, and pharmaceutical discovery and development. He joined APR in 1995 as head of licensing and business development and was appointed CEO in 2002. Under his leadership, APR has brought its first product onto the market and developed a rich pipeline of product candidates. Paolo also was a founding partner, CEO and board member of the Institute for Pharmacokinetic and Analytical Studies AG (IPAS), a Swiss contract research organization, as well as CEO and board member of Farma Resa s.r.l., an Italian CRO. Paolo is a Chartered Financial Analyst (CFA) and has a bachelor’s degree in economics from the Commercial University Bocconi, Milan, Italy.

Gilles della Corte, M.D. (Chief Medical Officer)
Gilles Della Corte, M.D., joined Relief in September 2020 as Chief Medical Officer. At Relief, Gilles is responsible for the clinical development of RLF-100 in Europe and coordinating closely with NRx, which is responsible for clinical trials in the US, as well as interactions with and submissions to regulatory authorities. He brings over 40 years of professional experience, including 30 years in the biopharmaceutical industry. Gilles held several senior clinical research positions at Merck Serono (previously Serono), where he was responsible for the development from proof of concept to life cycle management of projects in several disease areas, including cardiology, rheumatology, oncology and endocrinology. Earlier in his career, he also held positions of increasing responsibility at several clinical research organizations (CROs), pharmaceutical and start-up companies, including Rhone-Poulenc-Rorer, Servier, Solvay Pharma, as well as Phoenix Life Sciences, Larime, Omnicare Clinical Research, Therapharm, and Anergis. In 2016, Dr. Della Corte founded Dellmed Consulting, providing strategic advice and hands-on support for clinical development in various therapeutic areas, such as dermatology, oncology, allergy, and for CRO selection for companies ranging from biotech start-ups to well established pharmaceutical companies. Gilles holds an M.D. from Paris-Sud University (Paris XI) and is a Board-certified cardiologist with ten years of hospital practice.
Jeremy Meinen (VP Finance and Administration)
Jeremy Meinen joined Relief as ad-interim Chief Financial Officer in April 2020 and now serves as principal finance and accounting officer. Prior to joining Relief, Jeremy provided financial consulting and controlling services to companies in various industries. He began his career in an international audit firm, where he held positions of increasing responsibility and scope over more than six years. Jeremy holds a Master of Science in finance from Bocconi University and a Bachelor of Arts degree in Business Administration from the University of Geneva. He is a Swiss certified public accountant.

Giorgio Reiner (Corporate Director R&D APR Applied Pharma Research)
Giorgio Reiner is the Chief Scientific Officer (CSO) and Head of Research & Development Operations of APR Applied Pharma Research S.A. He has over 25 years of work experience in Research and Development in areas including organic drug synthesis, pharmaceutical process development and analytical control. Mr. Reiner has joined APR in 2000 and currently serves as Chief Scientific Officer (CSO) and Head of Research & Development Operations. Mr. Reiner holds a graduate degree in pharmaceutical chemistry and technology from the University of Pharmacy in Milan, Italy. He has completed post graduate courses in toxicology as well as in cosmetic technology. Mr. Reiner is author of scientific publications and inventor or co-inventor of several patents covering synthesis processes, drug delivery technologies and pharmaceutical compositions and formulations.

Board of Directors biographies

Raghuram (Ram) Selvaraju, PhD, MBA (Chairman of the Board)
Raghuram Selvaraju is a Managing Director of Equity Research at H.C. Wainwright & Co., a leading full-service investment bank headquartered in New York, USA, whose research focuses on the healthcare sector. He has over 15 years of experience on Wall Street and previously was a pharmaceutical researcher at Serono in Switzerland. In addition, Ram has appeared numerous times on Bloomberg, CNBC, Business News Network and BTV where he discussed drug development trends, healthcare reform policy, and pharma and biotech M&A. Prior to joining H.C. Wainwright, he held Senior Research positions at MLV & Co., Aegis Capital, Hapoalim Securities USA and Rodman & Renshaw LLC. Ram was Head of Healthcare Equity Research at both Aegis and Hapoalim Securities. He became the youngest-ever recipient of the Serono Pharmaceutical Research Institute's Inventorship Award for exceptional innovation and creativity in 2003. Ram earned his Ph.D. in cellular immunology and molecular neuroscience and an M.S. in molecular biology from the University of Geneva in Switzerland on the basis of his drug development research. Ram holds an M.B.A. from the Cornell University accelerated one-year program for scientists and engineers. He also has a B.S. in biological sciences and technical writing from Carnegie Mellon University.

Tom Plitz (Member of the Board)
Tom Plitz is Chief Executive Officer of Chord Therapeutics SA, a privately held biopharmaceutical firm based in Geneva, Switzerland. He has more than two decades of experience in pharmaceutical R&D, most recently as Chief Scientific Officer of the rare disease company Wilson Therapeutics. Wilson Therapeutics was acquired for USD 855 mn by Alexion Pharmaceuticals in April 2018. Tom’s previous assignments include senior roles at Serono, Merck, and Shire, where he worked across multiple therapeutic areas, including neuroinflammatory, metabolic, and rare diseases. Tom holds a Ph.D. from Technical University of Munich, Germany.

Please see important research disclosures at the end of this document
Patrice P. Jean (Member of the Board)
Dr. Patrice P. Jean is the Chair of the Life Sciences Practice at Hughes Hubbard & Reed, an international law firm based in New York City. She has over a decade of experience counselling leading and startup pharmaceutical, chemical and biotechnology companies in all areas of patent law, including asserting and defending patent rights underlying core technologies and innovations. Dr. Jean graduated summa cum laude from Xavier University of Louisiana in 1993 with a degree in biochemistry, and she holds a Ph.D. in molecular biology from Princeton University. She graduated from Columbia University School of Law in 2002, where she was Editor-in-Chief of the Columbia Science & Technology Law Review. Dr. Jean currently serves as Vice-President of the New York Intellectual Property Law Education Foundation and is a Board member of the New York Intellectual Property Law Association.

Paolo Galfetti (President of Relief Europe)
See biography above.
## RELIEF THERAPEUTICS

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</tbody>
</table>

**Income Statement**

**REVENUES**

**GROSS PROFIT**

**RESEARCH & DEVELOPMENT**

**OTHER GAINS/LOSSES**

**OPERATING COSTS**

**OPERATING COSTS (PER MONTH)**

**EBITDA**

**INCOME STATEMENT**

**PRODUCT SALES (INCL. PARTNER SALES)**

**PRODUCT SALES (RELIEF THERAPEUTICS)**

**ROYALTIES**

**UPFRONT AND MILESTONE PAYMENTS**

**OTHER REVENUES**

**COSTS**

**CHANGE (%)**

**EPS (CHF)**

**TAXES**

**MARGIN (%)**

**OPERATING RESULT**

**IMPARIEMENT (LOSS)/REVERSAL**

**D&A**

**NET FINANCIAL INCOME/(EXPENSES)**

**PROFIT-LOSS BEFORE TAXES BEFORE PROFIT SPLIT**

**GAIN FROM DISPOSAL OF A SUBSIDIARY**

**PROFIT SPLIT AGREEMENT WITH NRX & ACER**

**PROFIT-LOSS BEFORE TAXES - AFTER PROFIT SPLIT**

**TAXES**

**NET PROFIT LOSS**

**EPS (CHF)**

**CHANGE (%)**

**ESTIMATES AS OF 22 NOVEMBER 2021**

**SOURCE:** VALUATIONLAB ESTIMATES

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Please see important research disclosures at the end of this document.
NOTE: With cash and cash equivalents of CHF 45 mn, Relief expects to fund operations into late 2023 without factoring in potential revenues from RLF-100 sales, which could commence in 2022 and the CHF 50 mn share subscription facility with GEM. The company is fully financed to successfully complete the US “AVICOVID-2” trial of RLF-100 INHALED in prevention COVID-19 related ARDS (started in February 2021) as well as the planned EU RLF-100 trials expected to start in 2022. Relief may need a maximum of CHF 25-30 mn in additional funding to reach positive operating cash flow status before the end of 2024, which is dependent upon timely approval of ACER-001 in the US.
**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. Additional protection is provided by orphan drug status (10 years in EU, 7 years in US). The average Research & Development Phase takes 8-14 years, leading to an effective Return Phase of 6-12 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.

### 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.

<table>
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<tr>
<th>DEVELOPMENT STAGE</th>
<th>AIM</th>
<th>WHAT / WHO</th>
<th>SUCCESS PROBABILITY (%)</th>
<th>COSTS (USD MN)</th>
<th>ROYALTIES (%)</th>
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<td>ESTABLISH THE TESTING PROTOCOL</td>
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<td>OPTIMAL DOSEAGE</td>
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<td>PHASE III</td>
<td>EVALUATE OVERALL BENEFIT/RISK</td>
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**SOURCE:** VALUATIONLAB, TUFTS, FDA, EMA, CLINICALTRIALS.GOV
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| 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) |
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