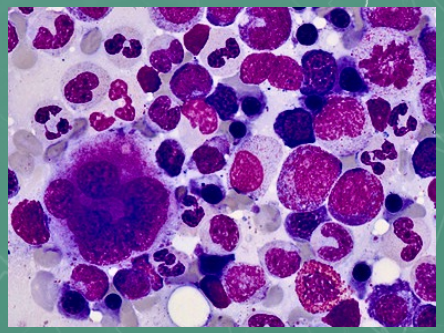
Velvio

We accelerate Brain Repair

Breakthrough for Amyotrophic Lateral Sclerosis (ALS) Patients:

Pulsed Bone Marrow Stem Cell Mobilization by G-CSF leads to Slow Disease Progression and Long-Time Survival in ALS-Patients

Fundraising for Pivotal Clinical Phase 2b/3 to get Approval



- *Munich / Regensburg - Germany*
- *February 2024*

Velvio‘s “G-CSF to treat ALS“ - Executive Summary

Idea: G-CSF bone marrow stem cell mobilization is an effective Therapy in ALS

- Clinical pilot data show slow disease progression & improved survival
- Biomarker panel validates longterm survivors

Approach: Develop patch pump to perform pivotal clinical trial for approval in ALS

1. Complete patch pump in 2025
2. Initiate Phase 2b/3 trial with ≥ 130 ALS patients in Q1/2026 with novel adaptive trial
3. Achieve conditional FDA / EMA approval in 2026/27

Market:

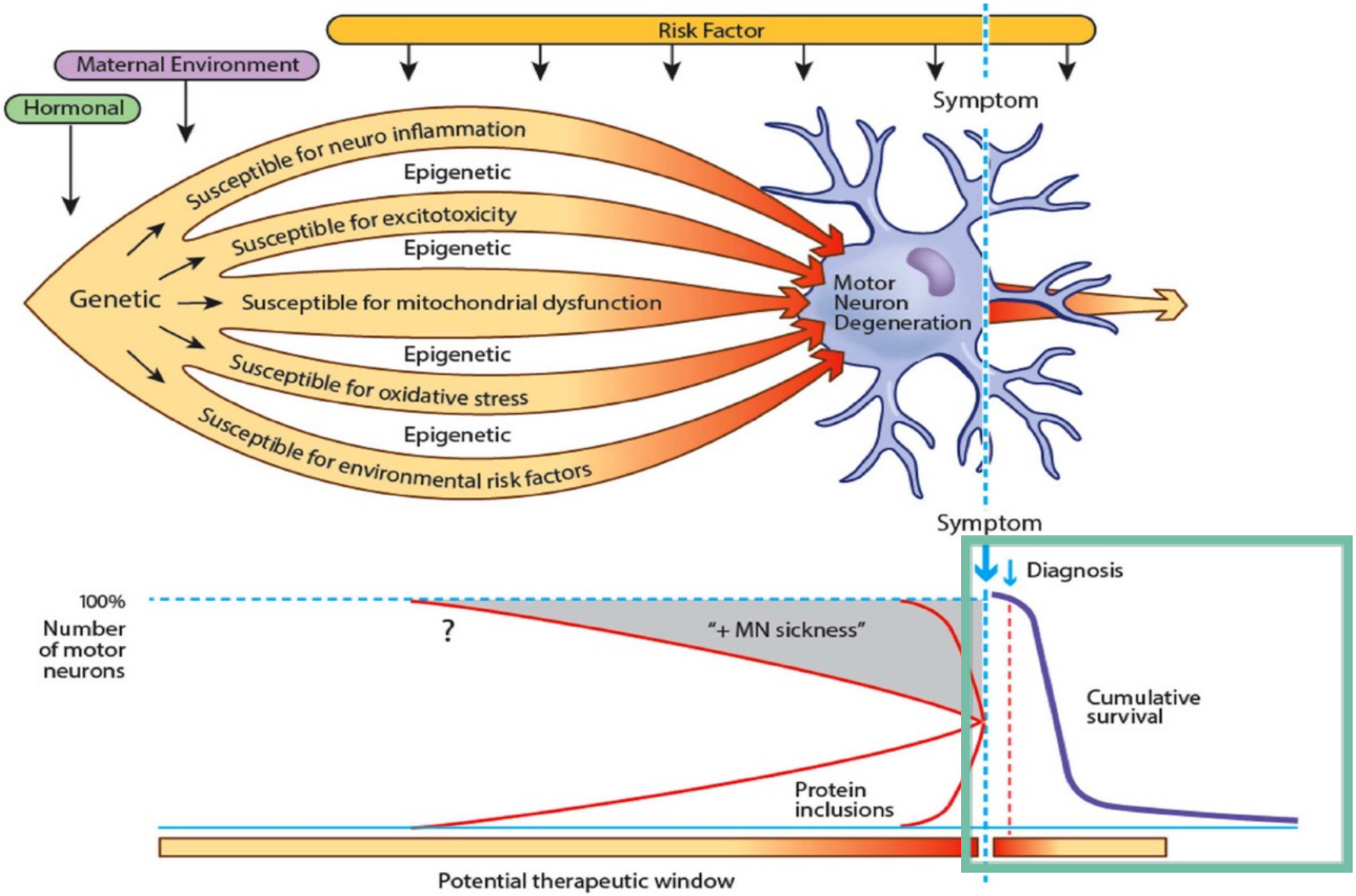
- Exclusivity by Orphan Drug Protection in EU / US and User (Label of Approval)
- Projecting $500M/year sales in 7 MM

IP: Exclusivity on drug-device combination for > 10 yrs

Financing: Velvio is raising € 50 M

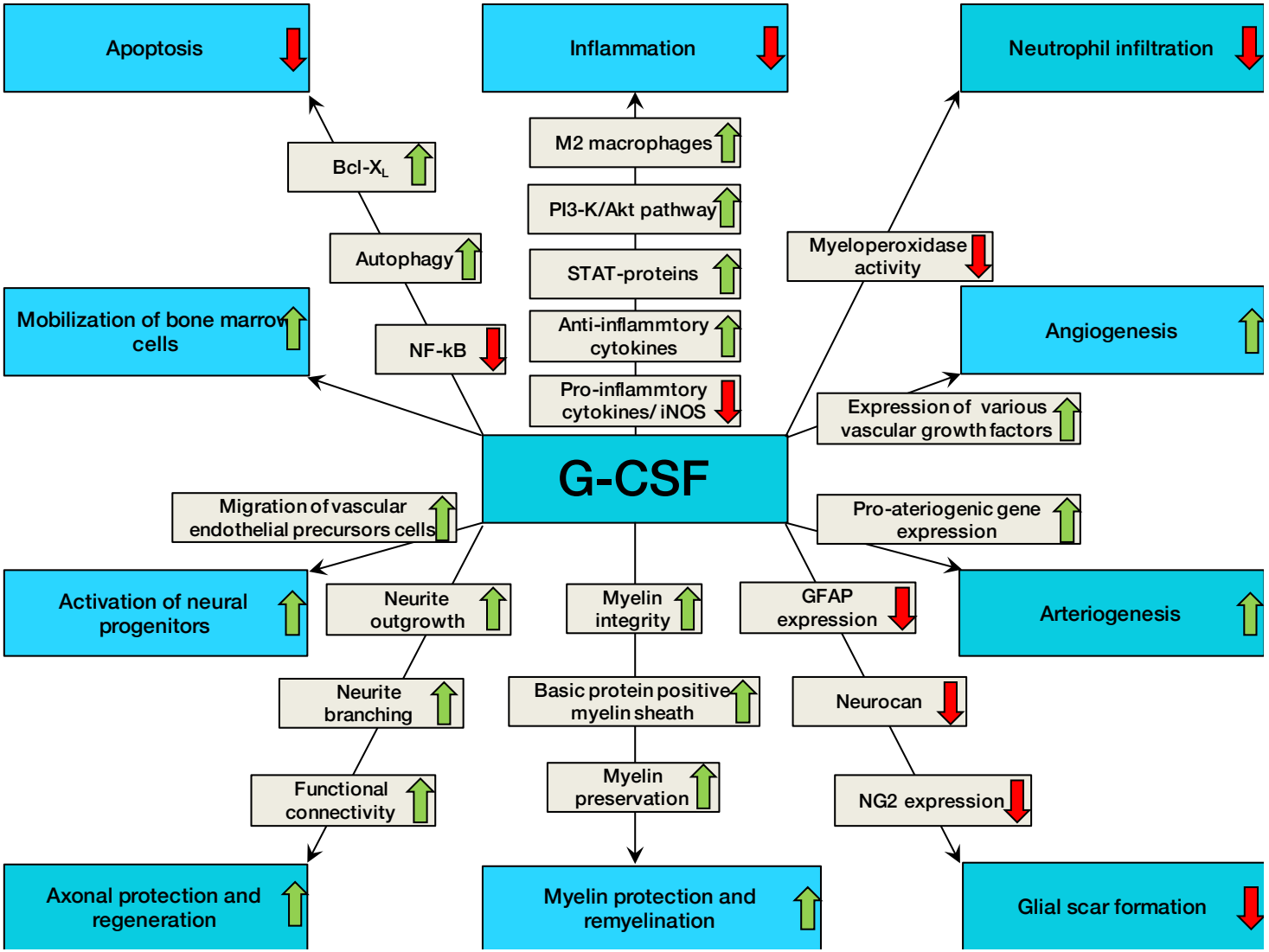
- € 23-24 M to develop drug-device combination incl. CMC, standardize biomarker panel
- € 27-28 M for registrational Phase 2b/3 trial for conditional FDA/EMA approval in 2027

ALS - a grave neurodegenerative disease of complex & long pathophysiology - needs a powerful and comprehensive longtime intervention to stop it



Modified from Eisen et al., 2014

Filgrastim (G-CSF) acts at many targets as highly comprehensive treatment and therefore is a promising candidate for long-lasting ALS-Therapy



Stephanie Wallner et al: **Front Neurology 2015, Stephanie Wallner et al: Drug Discovery 2021**

G-CSF stands for > 30 years of safety and survival in oncology – transfer to ALS needs to show efficacy and long-time tolerance

- **Granulocyte colony-stimulating factor**
- **K. Welte 1985, Pediatrician, MHH - Germany**
- **Human 19.6 kD glycoprotein**
- **On the market since 1991 ("Neupogen")**

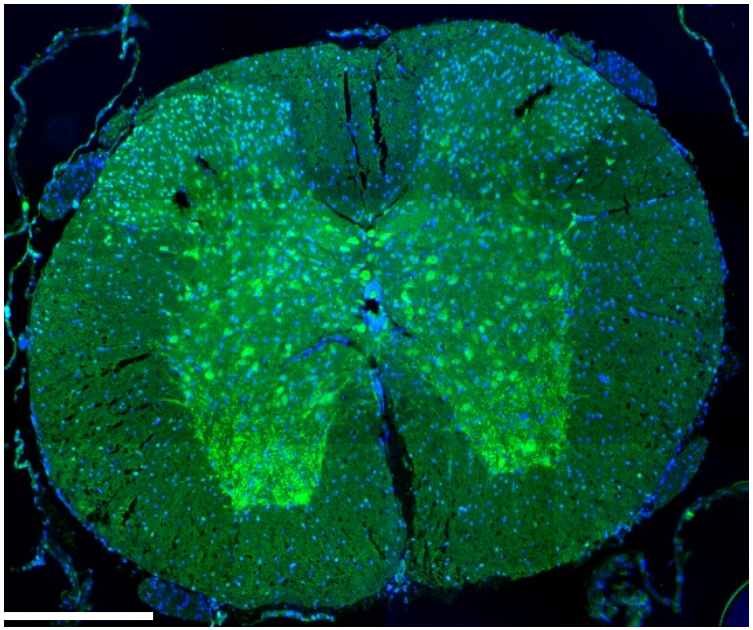
Biological Function: Stimulates survival / proliferation and mobilizes hematopoietic stem and progenitor cells from bone marrow.

Existing indications: Neutropenia in oncology, prevention & treatment infectious complications of chemotherapy, stem cell transplantation

Side effects: bone and muscle pain, well known safety profile

New indication ALS: treatment concept of long lasting stem cell mobilization, needs early start and upper dosing

The G-CSF receptor is expressed in motor neurons of the spinal cord



***From: Pitzer et al., 2008**

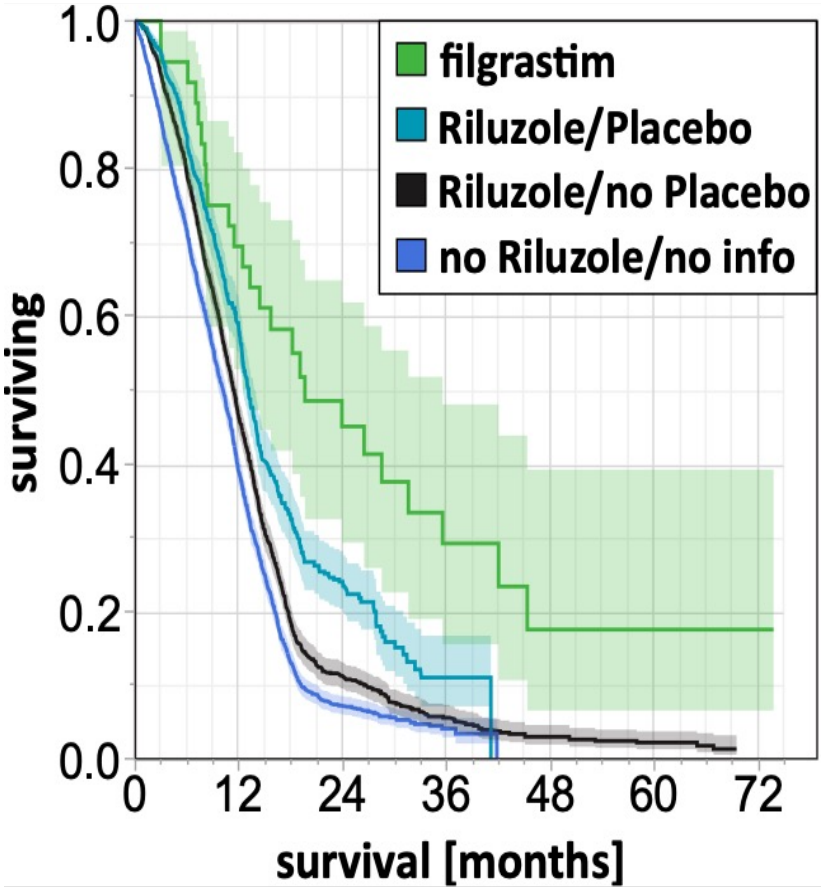
* Pitzer, C.; Krüger, C.; Plaas, C.; Kirsch, F.; Dittgen, T.; Müller, R.; Laage, R.; Kastner, S.; Suess, S.; Spoelgen, R.; et al. Granulocyte-Colony Stimulating Factor Improves Outcome in a Mouse Model of Amyotrophic Lateral Sclerosis. *Brain* **2008**, *131*, 3335–3347, doi:10.1093/brain/awn243.

Uni Regensburg treated 36 ALS patients and compared outcomes to current standard therapy - collected in the PRO-ACT *,**,*** database

G-CSF led to robust and relevant survival-benefit - strongly associated to initial functional ALS-FRS-R score and age - less to gender, latency to first symptoms and site of manifestation

Analysis in matched pairs (1 G-CSF: 10 PRO-ACT) reveals a 50% survival benefit for all G-CSF treated patients (median survival):

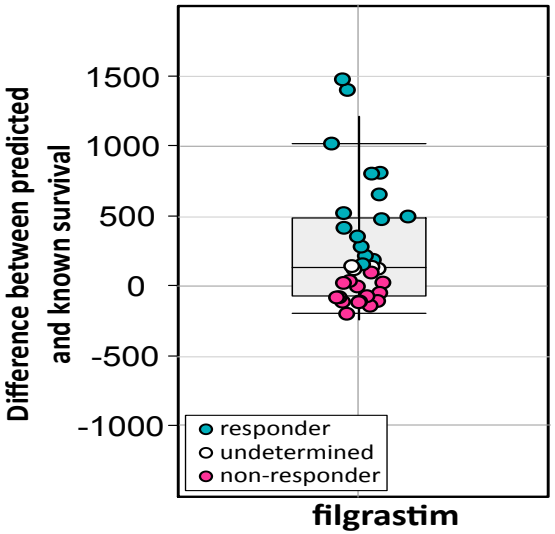
PRO-ACT*.* 373 days vs. G-CSF 596 days (p<0.001)**
rp-PRO-ACT 403 days vs G-CSF 596 days (p<0.005)**



*Johannesen S, ..., Bruun T-H, Ferguson AR, Bogdahn U. Frontiers; 2021 Mar 18;12. ** rp means population with Riluzol and placebo only;***Data used in the preparation of this article were obtained from the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) Database. The data available in the PRO-ACT Database have been volunteered by PRO-ACT Consortium members." alsinfo@alsa-national.org

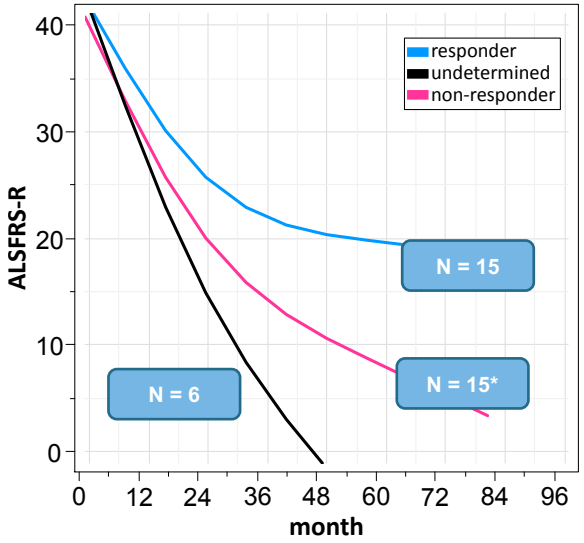
40% of patients had exceptional strong G-CSF response - identified by PRO-ACT* modeling – with almost 4-fold survival

PRO-ACT Modeling



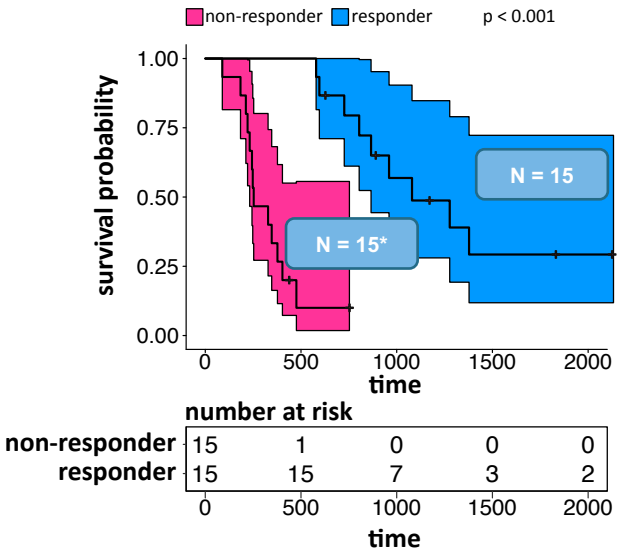
Modelling with PRO-ACT** Database, allowed to predict outcome in 36 G-CSF-treated ALS patients: however, survival was either lower than predicted (called non-responder) or higher than predicted (called responder). These populations were further compared

ALS Progression.



ALS patients` clinical progression is expressed by the slope of ALS-FRS-R scores over time, and is normally between 0,90 and 0,97/month. In responder patients slope got increasingly flatter – from 0.24 / mo (up to year 3) to 0,12 / mo further on, revealing a strong stabilization

ALS Survival.

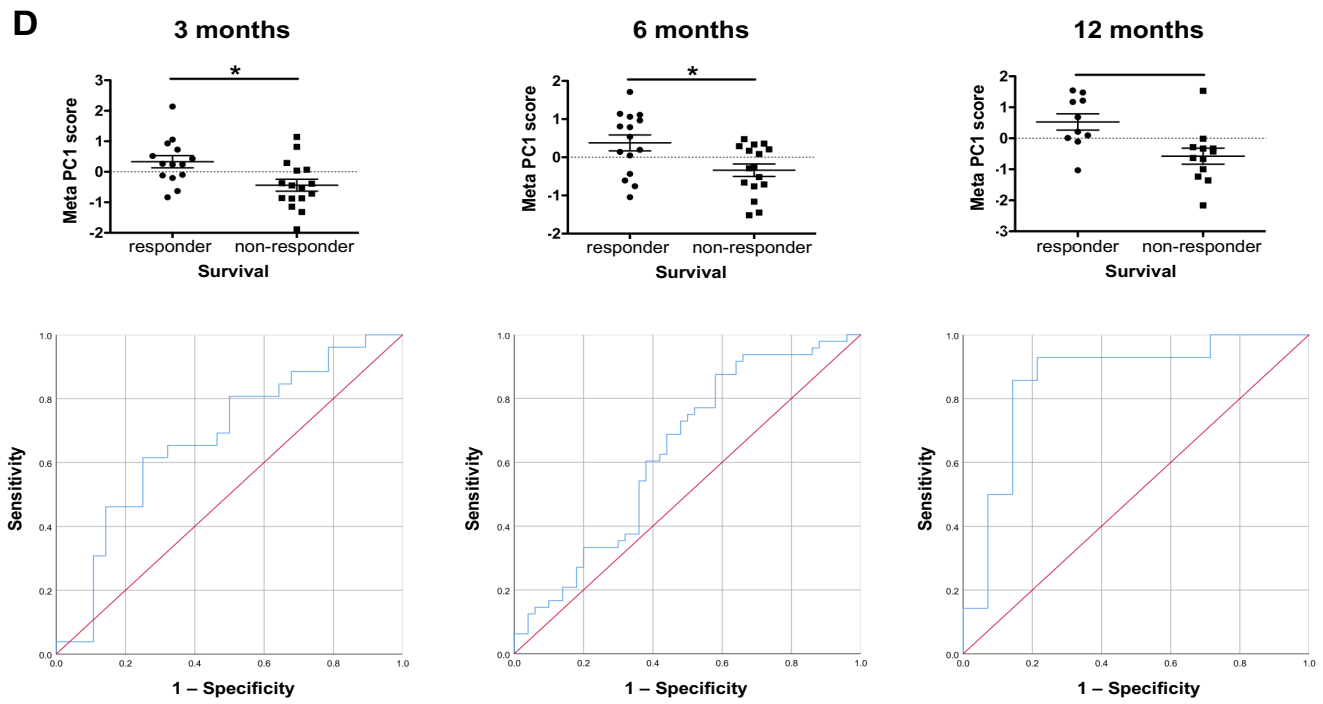


ALS Patients`survival is typically expressed in Kaplan–Meier plots. Responders had a ***median survival*** of 3.8 years* (blue) from start of treatment (N=15). Non-responders ha a median survival of < 1 year (red) (N=15). In PRO-ACT** patients would have had a median survival of *: 1.1 years

Johannesen S, ..., Bruun T-H, Ferguson AR, Bogdahn U. Frontiers; 2021 Mar 18;12. **Data used in the preparation of this article were obtained from the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) Database. The data available in the PRO-ACT Database have been volunteered by PRO-ACT Consortium members." alsinfo@alsa-national.org

Velvio´s Biomarker panel reflecting brain structure, inflammation and stem cell activity could predict response within 3 months of G-CSF treatment

- Biomarkers confirm MoA & significantly predict treatment outcome after 3, 6 and 12 months of G-CSF therapy
- Biomarkers may enable an adaptive trial concept to identify / enrich for potential „super responders“
- Biomarkers will also serve for treatment safety and may be part of the approval label



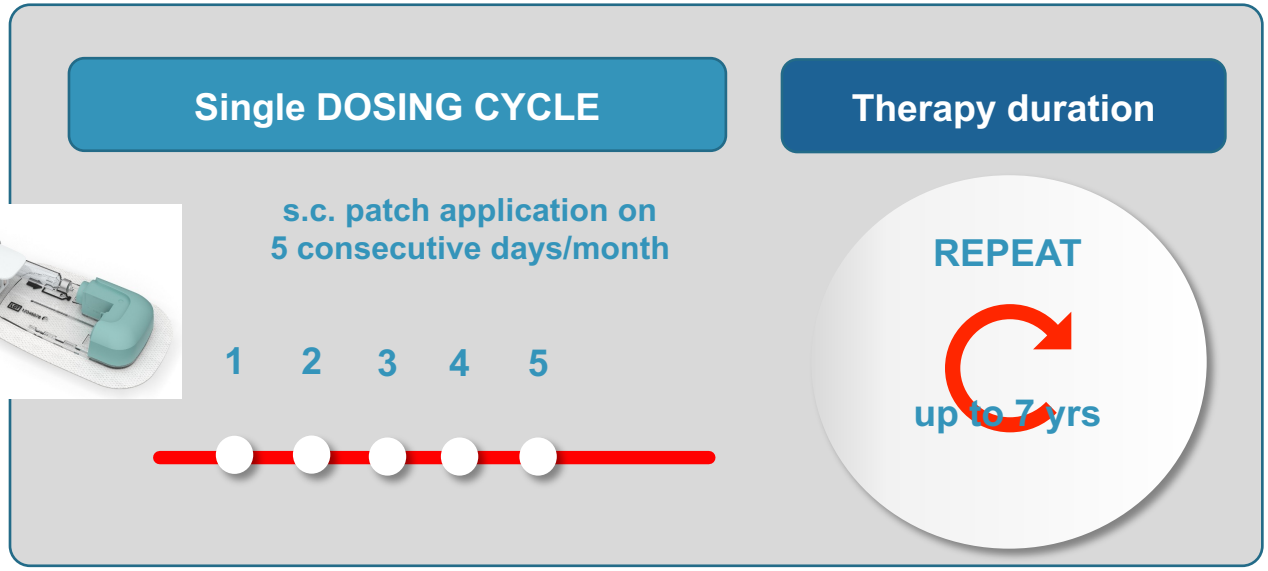
Cooperation with Russel Huie, Adam Ferguson, UCSF, San Francisco

Testing ROC (sensitivity / specificity)

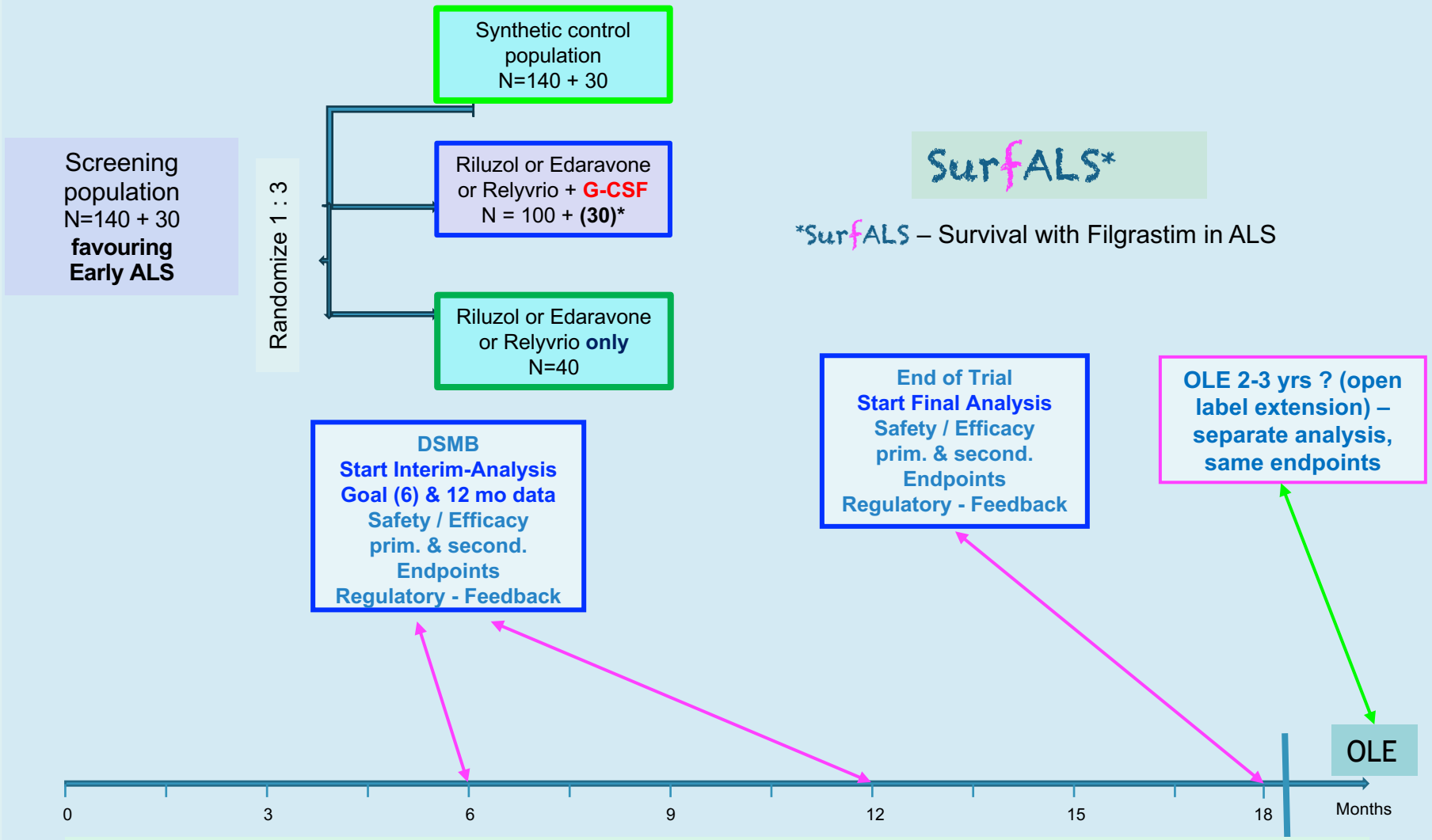
*Johannesen S, ..., Bruun T-H, Ferguson AR, Bogdahn U. Frontiers; 2021 Mar 18;12.

Velvio is determined to translate these data from stem cell mobilization by G-CSF to an approved therapy in ALS - Patients

- **Can we translate these pilot data in a pivotal clinical Phase 2b/3 trial with pulsed G-CSF - application and receive FDA / EMA approval**
- **Aim: achieve a very low disease progression and improve survival by factor 3 to 4 with high QoL**
- **Use a patch pump instead of individual syringes to**
  - Mitigate G-CSF - side effects
  - Improve feasibility and adherence
  - Establish safe home-based long-term biomarker guided stem cell therapy
  - Employ guidance by experienced team including Neurologists and Hematologists



How does Velvio want to pursue the pivotal clinical trial ?



Clinical Trial - Regulatory: Rolling Review

All relevant Partners are already on board

Velvio

Velvio
We accelerate Brain Repair

- Project Lead
- Scientific Know how / Clinical Data
- Clinical Trial planning and conduct
- Regulatory Processes EMA / FDA
- MAA-/NDA – Holder
- Project Funding (R&D Phase)
- R&D – Label Extensions

Launch ALS-Filgrastim in US and EU in ALS Centers (Neurologists and Hematologists)

CRO-/Clin. Partner

- Clinical Trial to include patients early in their disease - who benefit most from Thx

Pharma Partner* teva

- API / Bulk Substance Supply
- Support Regulatory Submissions (IND, NDA/MAA)
- Optional: Marketing & Sales: North America, Europe

CMC Partner

ten 23

- CMC and Fill & Finish Development
- Mfc. and Supply of pre-filled cartridges (for Device)
- Support Regulatory Submissions (IND, NDA/MAA)
- Mfc. & commercial supply of final Drug Product

MedTech / Device Partner*

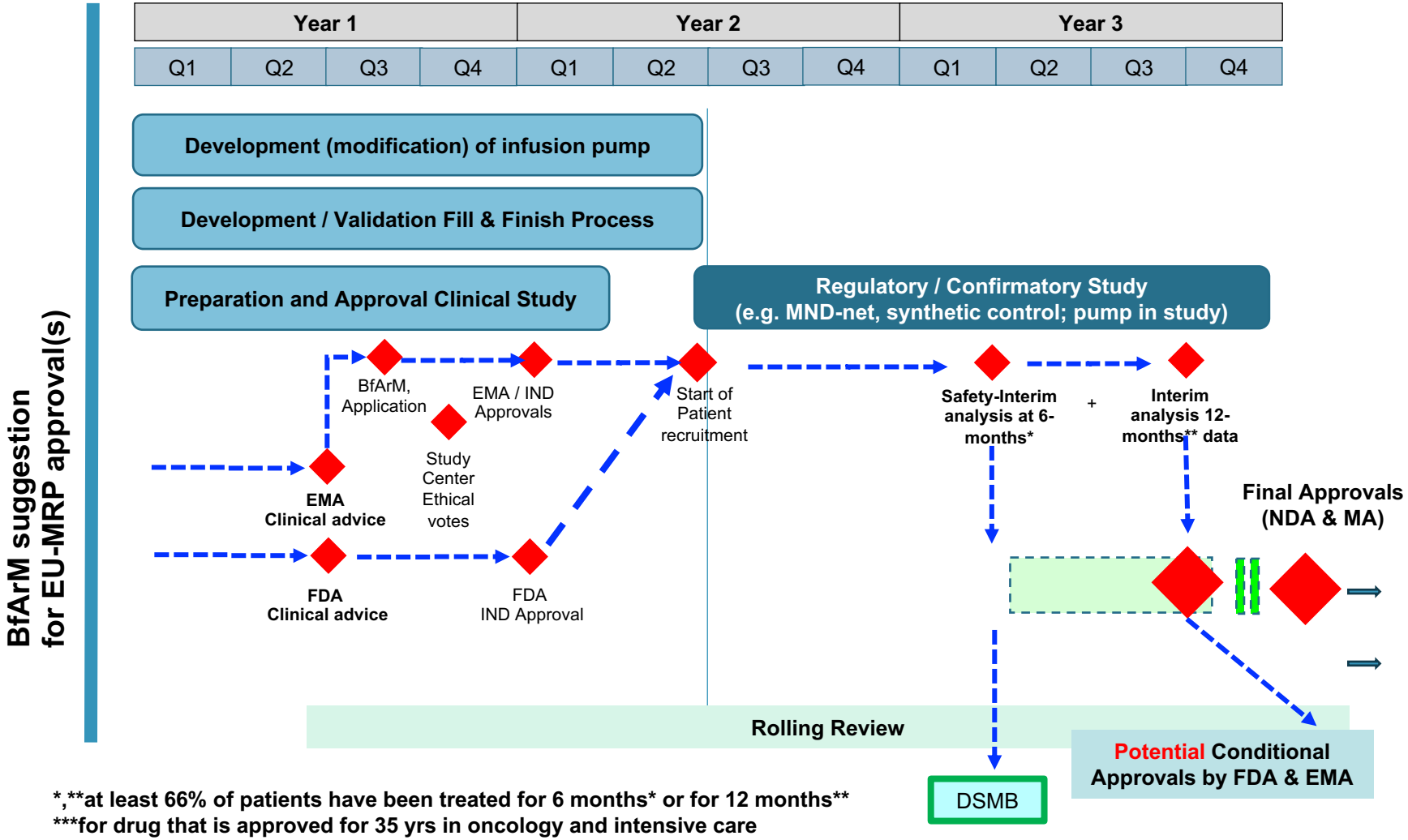
SENSILE MEDICAL
A Gerresheimer Company

- Device IP protection
- Medical Device Adaptation to G-CSF protocol
- Support Regulatory Submissions (IND)
- Device Supply for Clinical Study
- Support Regulatory Submissions (NDA/MAA)
- Market Supply of Patch Pump & Disposables

Timelines for this Neuro – Repair Project are rather short!

G-CSF in ALS / pivotal Phase 2b/3 to obtain Conditional Approval***

Development of Filgrastim for ALS patientswith Filgrastim + wearable infusion pump



*,**at least 66% of patients have been treated for 6 months* or for 12 months**
***for drug that is approved for 35 yrs in oncology and intensive care

The IP and Market Protection are achieved via Medical Device IP and extensive scientific and clinical know how (biomarkers, regul. labelling)

- **Orphan Drug Designation for G-CSF in ALS granted**
  - USA: 14-4618
  - Europe: EU/3/08/532
- **Clinical Data Protection / Market Exclusivity**
  - European Union: 8 years ODD / + 2 years + 1 year for new indication.
  - United States: 3 years for a new CE indication; 8 years ODD *(12 years for new biological products)*
  - Japan / China: 6 years
- **Medical Device Patent Family (compare to Insulin pumps)**
  - **Exclusive** wearable patch pump is protected by a patent family (latest expiry date is 2031)
  - **Further new IP** in development of Drug-Device combination, e.g. individual dosing
  -
- **User (Label) ‚Exclusivity‘**
  - Approved regulatory label shall restrict patient managment to ALS centers (joint neurological with hematological care) capable to safely monitor treatment response and adjust dosimetry / treatment intervals based on the biomarker panel developed by Velvio

Velvio`s Funding Needs for Operations and Project Performance

G-CSF in ALS

	Y-1	Y-2	Y-3
Velvio Ops: personnel, premises (lab & office), equipment, materials, utilities/services, biomarker program, IP/Legal, Consulting, Funding (EUR M)	5.5 – 6		9.5 – 10
Drug Product and Device Development			
Device development with API and patient profile	CMO 1		
API (G-CSF) / Fill & Finish development	CMO 2		
Clinical study preparation	*1 Velvio	*2	*3
Clinical study (FDA/EMA)		*1	Velvio: ALS Study
Application for Approval (NDA/MAA)			*2 cNDA/ cMA *3
Project costs (EUR M)	17.5 – 18		17.5 – 18
Total (EUR M)	23 – 24		27 – 28
		Total over 3 years: 50 - 52 EUR m	

*1 **FDA/EMA Clinical Advice**

*1 **FDA IND approval**
(chance of registry trial)

*2 **US FDA IND application**

*2 **Potential conditional approval**
6 months interim data

*3 **Start of confirmatory clinical trial**

*3 **Potential conditional approval**
12 months interim data

Project - Milestones and Funding Steps

1st step: 23 - 24 M EUR will enable FDA/EMA Clinical Advice, Drug Product and Device Development, Clinical trial protocol & biomarker program, IND approval and Trial Site selection / initiation

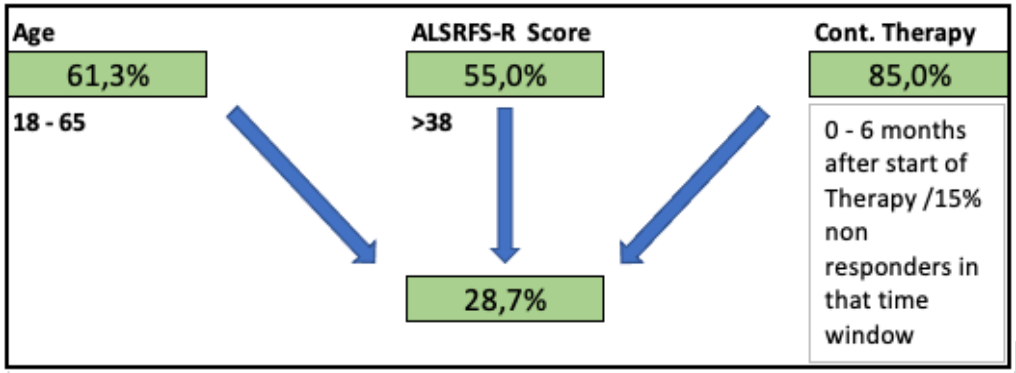
2nd step: 27 - 28 M EUR will lead to regulatory approval and commercialization capabilites:
Phase 2b trial conduct, clinical biomarker program, NDA/MAA submissions, Publications, Pharma Partnering/Licensing

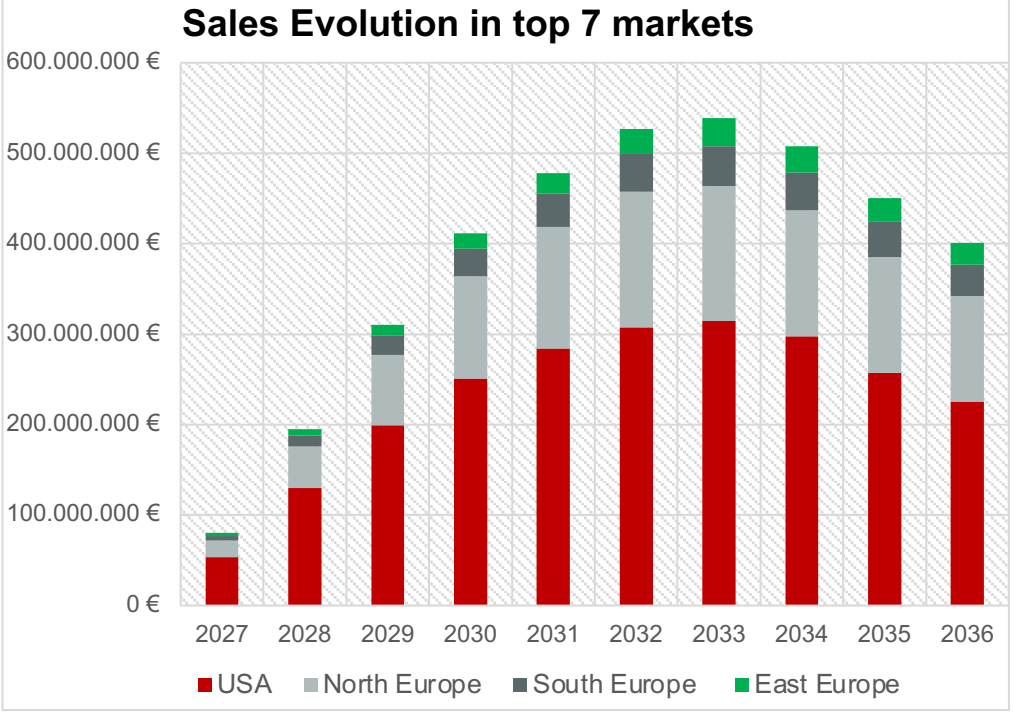
Velvio targets Peak Sales of half a billion in 7 major markets

Filgrastim Market Model in ALS

Key assumptions and outcome parameters – first outpatient long-time stem cell therapy

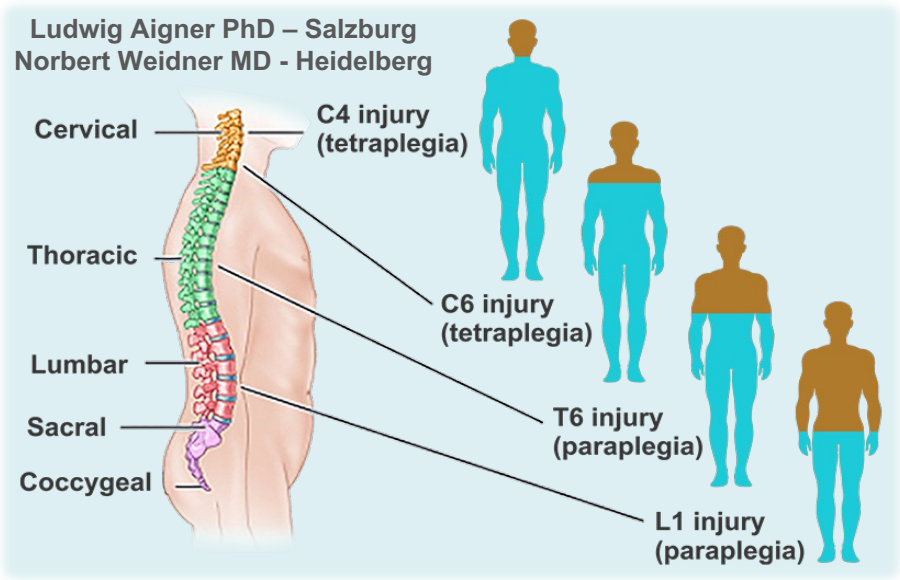
Conservative Estimates of Market Data for ALS	ALS
ALS Prevalence (2030)[1]	59.650
ALS Incidence (2030)[1]	23.860
Per 100.000	
US	*2,81*
North Europe	*2,81*
South Europe	*2,25*
East Europe	*2,53*
Patients eligible (2030)[2]	17.100
Eligible Patients in %	*28,7%*
Peak Patient Share[2]	42.5%
Median Life expectancy[2,3] *(from start of treatment)*	16 - 24 months
Patients treated (2030)[2]	8615
Median Treatment Duration[2]	**48** months
Launch Year (US)	Q1 2027
Launch Year (EU)	Q2 2027
End of Market exclusivity (US)	2034
End of Market exclusivity (EU)	2034
Ex-MNF price per year (US)	75.000 USD
Ex-MNF price per year (EU)	up to 37.000 €
Peak Sales (ex- mfc.)	**€ 538M**
Project NPV (18% non risk adjusted discount)	**€ 447M**

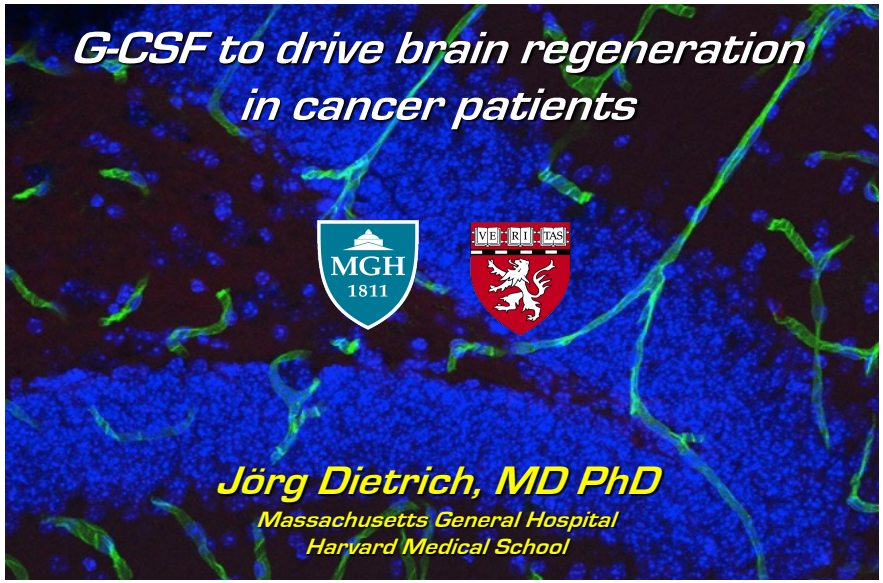




1. Public information & BGM Database and Estimates
2. BGM Database and estimates , Velvio Management's estimates

Velvio`s Filgrastim Product offers many attractive upsides





- This is the chance to establish *Long-Term Bone Marrow Stem Cell Mobilization* via ALS for other challenge indications like severe neurodegeneration (MSA), spinal cord injury and TBI, or ‚Chemobrain' in oncology

- Velvio asks to be active part of this breath-taking revolutionary therapeutic enterprise

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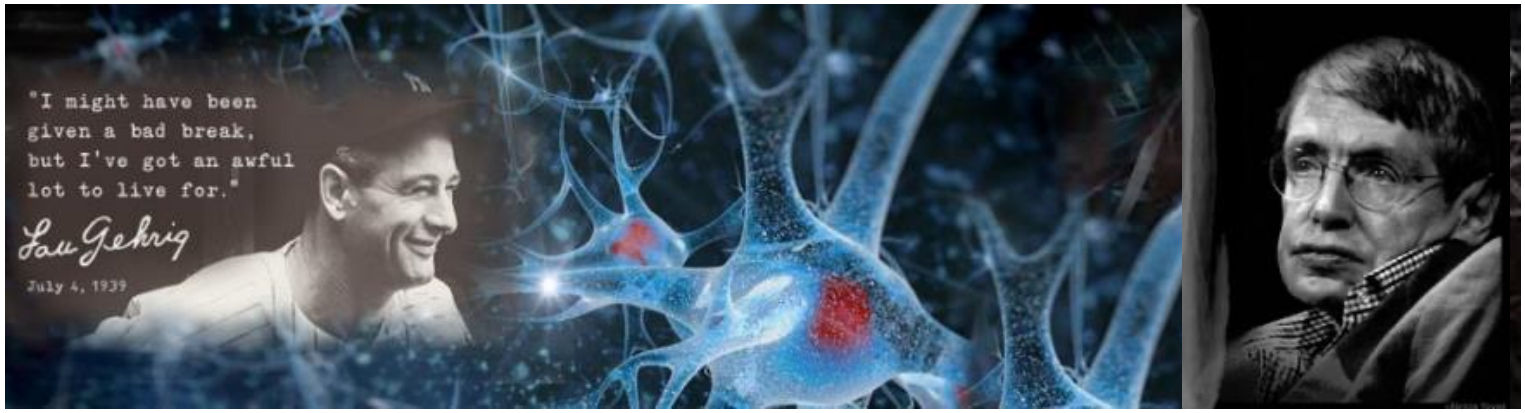
Appendix – Backup Slides

Velvio adresses a serious unmet clinical problem: ALS Patients still die loosing their motoneurons and their voluntary muscles within 2 to 3 years



- **Patients *progressively* lose their power to use their muscles, swallow and speak normally, or breathe and communicate easily, cognition remains fully alert!**
- **Overall median survival** from initial symptom with **21 – 31 months** post diagnosis **is poor** - **Incidence:** 2 - 2.5 / 100,000 and **Prevalence:** 4 – 6 / 100,000 [3] , **will increase by ~ 30%** in 7MM until 2040, median age varies in different populations
- Current **Standard of Care Therapies** Riluzole, Edaravone, Relyvrio have **delaying effects** **New developments** focus on mutations (mtSOD1), gene editing does not offer repair
- Individual **Life-Time Risk: 1 / 400**[4] correlates with **60 – 80,000 treated patients per year, thereof 37.000 – 50.000 in EU5, US, Japan**[5]
- **Patient - / Family costs peak around 150.000 € / year = 1.3 billion $ / year alone in US**

Velvio`s Vision: Let`s translate long-time stem cell mobilization to an approved therapy in ALS – Target Product Profile

Product Description	➢ Recombinant human Granulocyte Colony Stimulating Factor – G-CSF ➢ Binds to G-CSF-R, Dimerization and transmembrane signaling to JAK-STAT (Transcription), Lyn (Inflammation), Erk1/2 (MAP/ERK signaling) ➢ Proliferation of hematopoietic / other stem cells, anti-apoptotic, anti-inflammatory
Indication	➢ Early ALS, short latency from diagnosis, bulbar and spinal ALS ➢ Biological age <65 years - efficient stem cell mobilization ➢ modulated biomarker profile
Dose & Administration	➢ 60mio IU/ml per day on 5 consecutive days / month ➢ S.c. infusion (60 minutes) using wearable patch pump
Drug Product presentation	➢ Prefilled glass cartridge w / 1ml Filgrastim (600 μg/ml = 60 mio IU/ml) ➢ Device: wearable patch pump (reusable with electronics) using a disposable unit for each infusion (containing patch, needle and vacuum mechanism)
Efficacy	➢ Slow disease progression (monthly decline in ALS-FRS-R of 0.9 – 0.97 with currently approved medication to ALS-FRS-R of 0.12) under G-CSF treatment ➢ Increased overall survival - from currently: 24 months after 1st symptoms - to ≥ 4 years
Safety	➢ Very good tolerance and high safety (as reported in millions of patients in oncology indications), long-time use documented in 36 patients so far
Other benefit	➢ Increased Quality of Life during entire therapy period ➢ Change in brain structure, apoptosis protection, general anti-inflammatory effect
Positioning **Project Upside(s):**	➢ 'CNS Repair' by long-time bone marrow stimulation as a new therapeutic option for (early) ALS patients; ➢ Breakthrough facilitating extended survival in ALS with good quality of life ➢ Adding 'Chemobrain' (in cancer patients), Spinal Cord Injury, and other aggressive forms of neurodegeneration