TARGED

TARGETED ENZYME DELIVERY

FROM IDEA TO COMPANY

Kristof Vercruysse, CEO

Dutch Life Sciences 24 May 2022

FROM IDEA TO COMPANY

COEN MAAS

Discovering opportunities in multifactorial diseases

- Inventor of Microlyse
- Associate Professor in Immuno-thrombosis, UMC Utrecht
- 88 papers (H-index 29)

STEVEN DE MAAT

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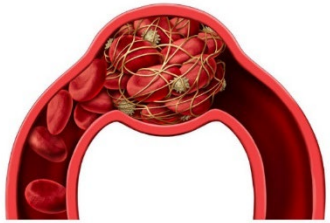

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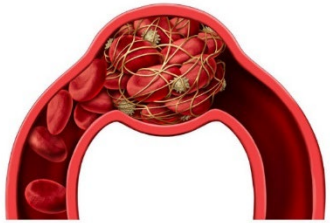
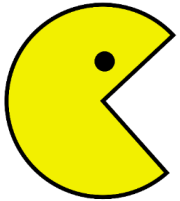


POTENTIAL NEW DRUG "MICROLYSE"



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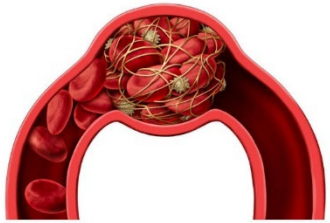

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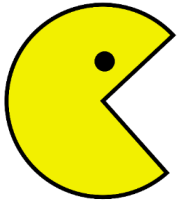

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Academic Progression: Need for Public Funding

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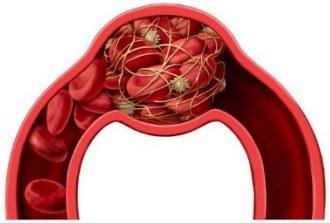

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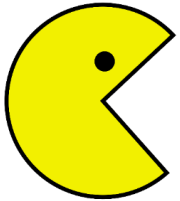

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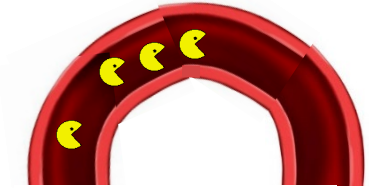
PROOF-OF-CONCEPT (MICE)



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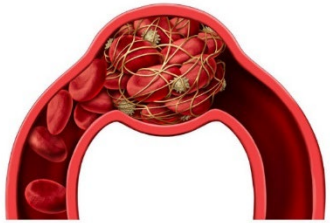

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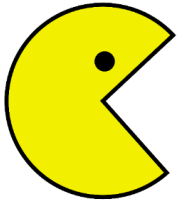

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PATENT

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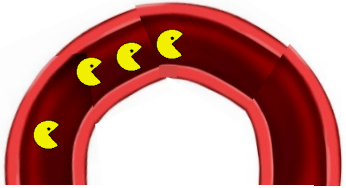


Academic Progression: Need for Public Funding

WE HAVE A PATENT, AND NOW WHAT?

1

Basic Research

Discovery shows promise to prevent, treat or cure a disease.

PUBLIC FUNDING

2

Translational Research

Additional research required to prove discovery is safe and effective.

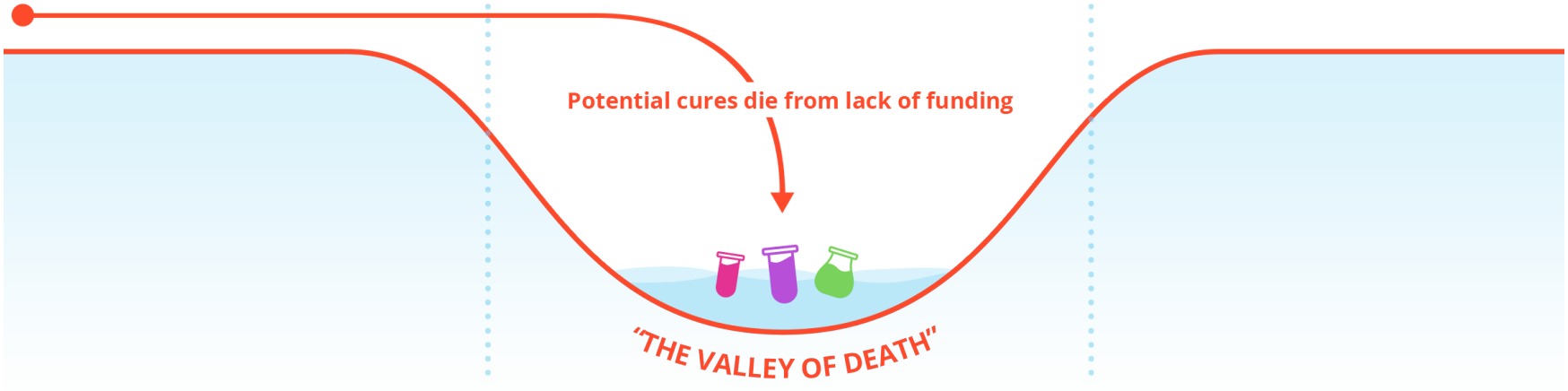
LACK OF FUNDING

3

Clinical Research

Several phases of clinical trials are conducted to receive FDA approval

PHARMA CO FUNDED



Dutch Life Science, Leiden

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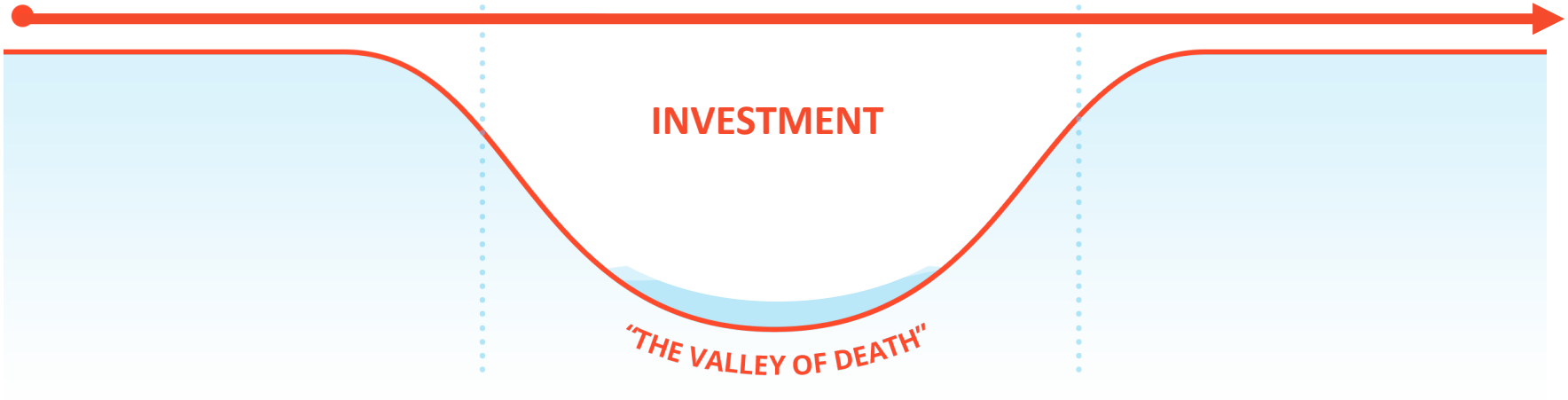

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FROM IDEA TO COMPANY

venture challenge

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MARC VAN MOORSEL

Translational business development in nanomedicines

- PhD student ‘Nanomedicine in Acute Ischemic Stroke’, UMC Utrecht

FROM IDEA TO COMPANY

venture challenge

IOVA BIOPHARMACEUTICALS
Towards vascular health

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FROM IDEA TO COMPANY

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VACANT
CEO

- Leading IOVA Biopharmaceuticals
- Interaction with investors
- Setting up a Strategy
- Comprehensive slide-deck

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- We need somebody with Development Expertise in the therapeutic area of interest (aTTP Orphan Indication)
- CEO had history of clinical development in aTTP – approached Kristof Vercruysse

FROM IDEA TO COMPANY

?

VACANT
CEO

COEN MAAS

STEVEN DE MAAT

MARC VAN MOORSEL

KRISTOF VERCRUYSSE

- Initial Strategy based on preliminary POC – Series A 18M Euro
- After discussion with well interested potential investors – final decision was not to move forward
- CEO stopped activities in mutual agreement
- 4 remaining team members decided to go for Seed Investment: 850 K Euro (Curie Capital, UHSF, FIRST (Managed by BGV)
- Management positions were divided

FROM IDEA TO COMPANY

KRISTOF VERCRUYSSE
CEO

Twenty years of experience in Drug Development

- 13 years in TTP field
- Brought multiple compounds from preclinical- to clinical POC

COEN MAAS
CSO

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Operational Lead

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FROM IDEA TO COMPANY

Seed Investment: Birth of TargED Biopharmaceuticals BV

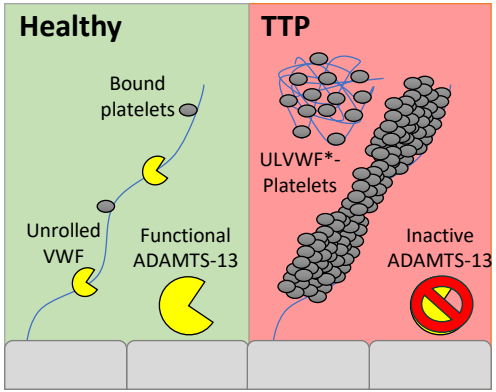
- POC's to generated
- Manufacturing to be translated from Academia to Industry
- Get additional non dilutive funding (TO1 – TO2 – MIT – PPS call)

Preparations for Series A funding:

- Microlyse = Thrombolytic agent – Unfortunately, nobody is happy with only breaking down blood clots
- Select your Therapeutic area(s) carefully
- Start Early in approaching Investors (even when not all information in hand)
- Select Investors based on Size of Investment rounds done, Experience, potential network to accelerate your development, Therapeutic area, etc …
- Have a comprehensive strategy: BELIEVE: be consistent!
- Build an understandable and reproducible story (someone will have to sell it to its own internal board)

CLINICAL UNMET NEED – autoimmune TTP

Microlyse could significantly reduce mortality and attack duration



The burden of TTP

- TTP patients lack functional ADAMTS13, leaving them at continuous risk for fibrin-poor microthrombosis
- Attacks result in organ failure and, ultimately, death
- Patients receive PEX, IS and Caplacizumab

Diagnosis

TTP symptoms
e.g. fever, neurological symptoms (60%), and renal insufficiency

Diagnosis of disease: ADAMTS13 activity <10%

Known TTP patient
1-10 cases/million

New TTP patients
1 case/million

Acquired TTP
(auto-antibodies) 95%

hTTP
5%

Remission of attack
Platelet count <100x10^9/L

Therapy

Plasma Exchange (PEX) +
1. Removing auto-antibodies
2. Removing blood clots
3. Replenishing ADAMTS13

Immunosuppressants (IS) +
Preventing auto-antibody production

Caplacizumab
Passively disrupting the platelet-VWF interaction

Current TTP-treatment with Caplacizumab is unsufficient

- Caplacizumab is given on top of PEX+IS and inhibits binding of platelets to VWF. It prevents microthrombi formation
- Still, TTP attacks last for 3-4 days
- *"Microlyse affects ' ' and could significantly reduce mortality and attack duration even more"* (KOL Prof. Knoebl)

	PEX + IS	PEX + IS + Caplacizumab
Mortality	~20%	~15%
Attack days	5	3-4
Plasma need	40L (€100K)	30L

***Abbreviatons –** UL-VWF = ultralarge Von Willebrand Factor ; hTTP = hereditary TTP ; PEX = plasma exchange ; IS = immunosupressants

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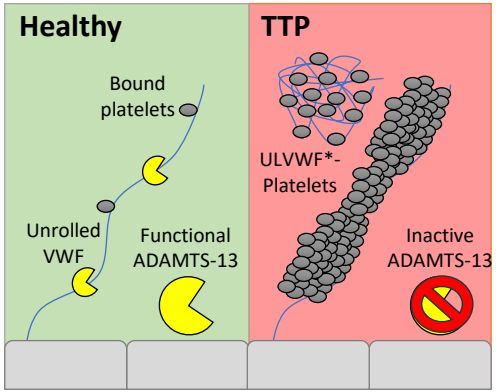

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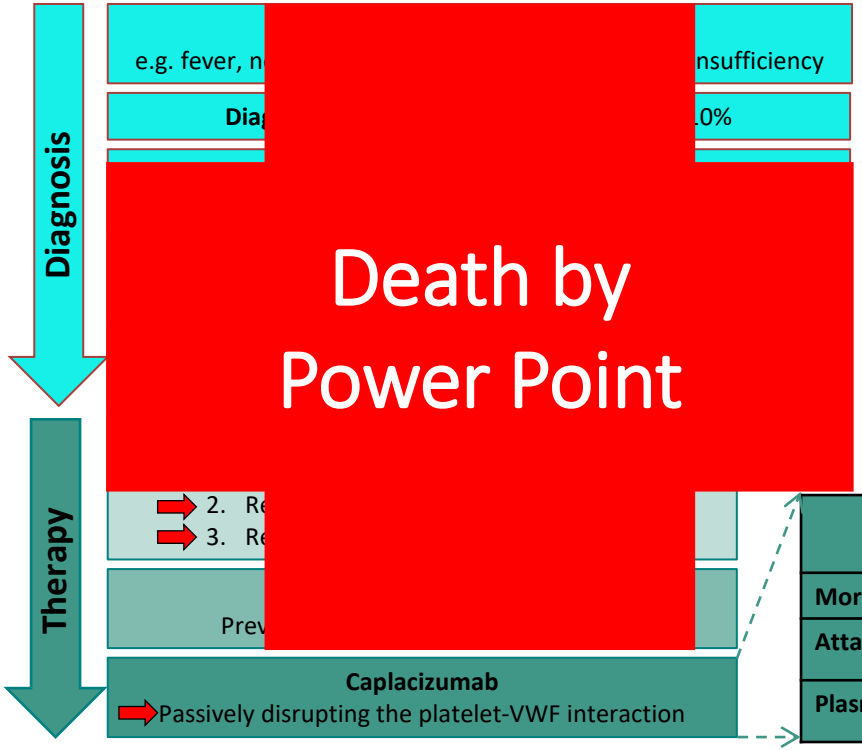

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Targeted, first-in-class fusion proteins for improved thrombolysis
TARGED
TARGETED ENZYME DELIVERY

EXECUTIVE SUMMARY

- Microlyse: effective thrombolysis for various forms of thrombosis
- Preclinically validated in two thrombotic indications
  - Acquired Thrombotic Thrombocytopenic Purpura (aTTP; orphan indication);
  - Acute ischemic stroke (AIS)
- Worldwide, exclusive license on IP, covering Microlyse and variant fusion proteins
- February 22nd, 2022: €39 million Series A investment
- Deliverables Series A (2022-2026):
  1. **Acute ischemic stroke:** POC data in large animal species, including bleeding and functional outcome (2023)
  2. **Independent of indication:** full CMC (non-GMP and GMP) and toxicology program (end 2023)
  3. **Independent of indication:** Phase I study in healthy volunteers, including preliminary POC in patients (2024)
  4. **Acquired Thrombotic Thrombocytopenic Purpura (aTTP):** successful completion of Pivotal study (mid 2026)
  5. **Acute Ischemic stroke:** successful completion of phase II POC study (end 2026)

COMPANY HISTORY

- Privately held company
- Founded July 2020
- Based in Utrecht, The Netherlands
- Investors: Andera Partners (FR), Curie Capital (NL), FIRST (NL), Fund+ (BEL), Hadean Ventures (NOR), Inkef Capital (NL), Sunstone Life Science Ventures (DEN), Utrecht Health Seed Fund (NL)

2015

Initial research grant (€450k)
Coen Maas, UMC Utrecht

2018

Patent filing
(WO/2019/185723): broad IP, covering fusion proteins for treatment of thrombosis

2019

Microlyse – lead compound selected
- Pilot in aTTP
- Pilot in AIS

2020

Spin-out from UMCUs
- Worldwide, exclusive license on IP
- €850.000 Seed Investment

2021

Deliverables Seed Investment
- Successful production in Yeast
- Preclinical PoC in aTTP
- Preclinical PoC in AIS
- €900.000 non-dilutive funding
- Manuscript Microlyse for aTTP

2022

Preclinical to clinical
- €39 million Series A
- Manuscript Microlyse for AIS *(expected Q2)*
- Tech transfer to Richter Helm (*expected Q2)*
- Additional preclinical validation in AIS

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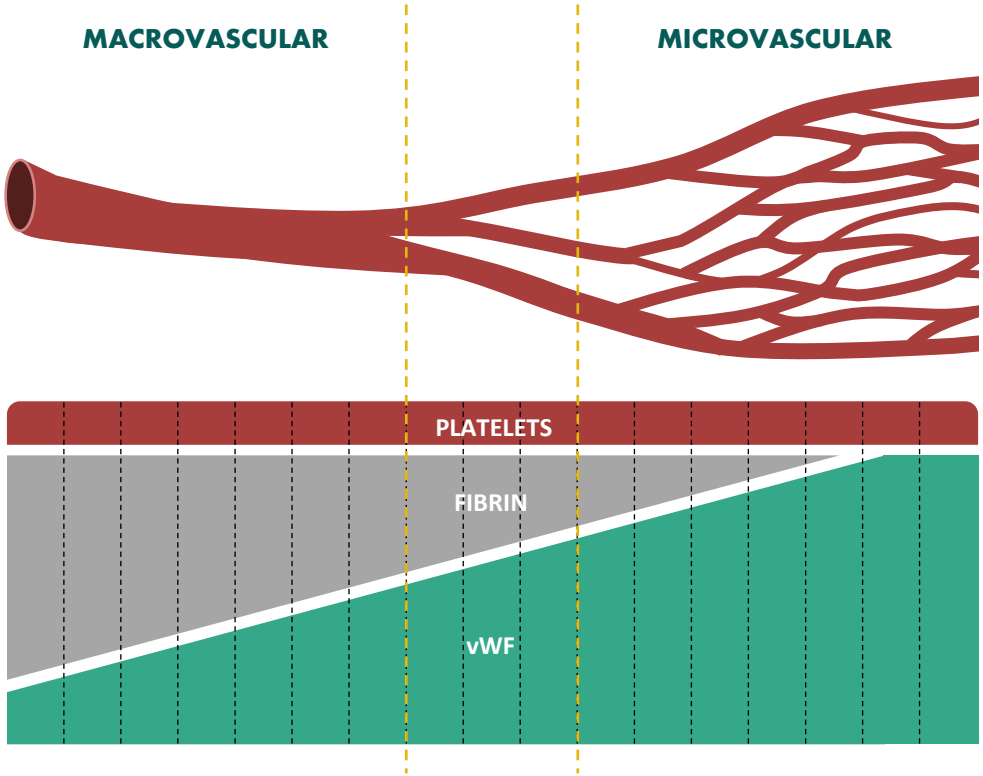
TARGETED ENZYME DELIVERY

Thrombosis: location within the vasculature determines clinical presentation and composition



Thrombotic indication

- Myocardial infarction (MI)
- Acute Ischemic Stroke (AIS)
- Deep vein thrombosis (DVT)

Typical composition

- Fibrin-rich
- vWF always present

Thrombotic indication

- Acquired TTP (aTTP)
- Thrombotic microangiopathy (TMA)
  - Drug related
  - Pregnancy related
  - Infection related

Typical composition

- No fibrin
- Only vWF

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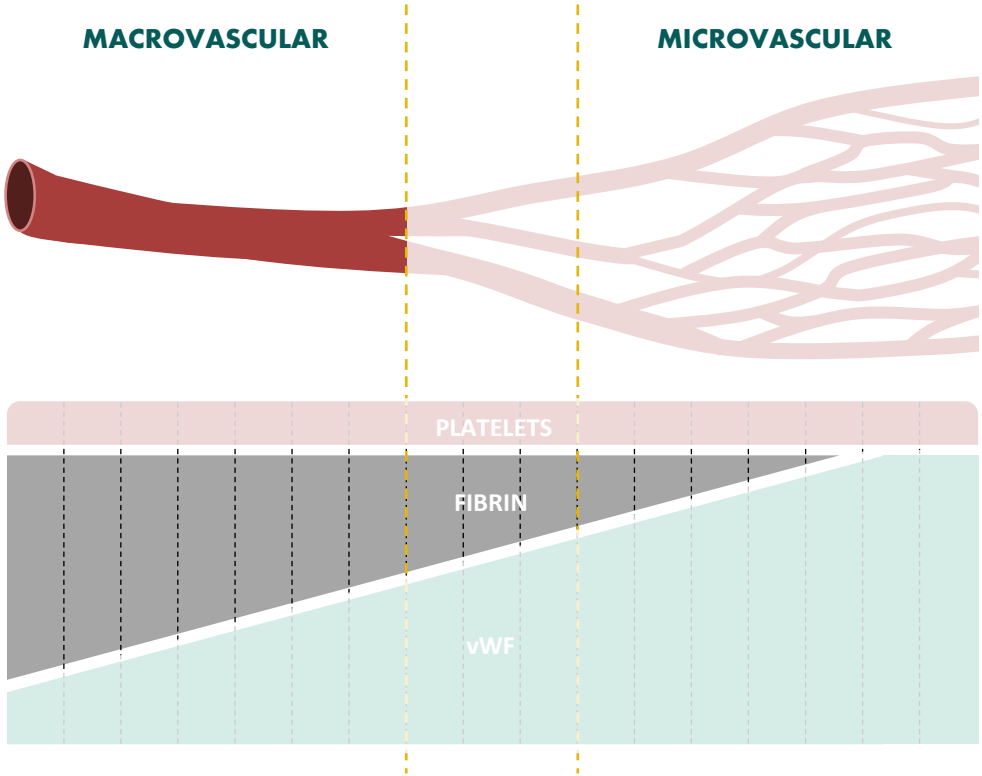
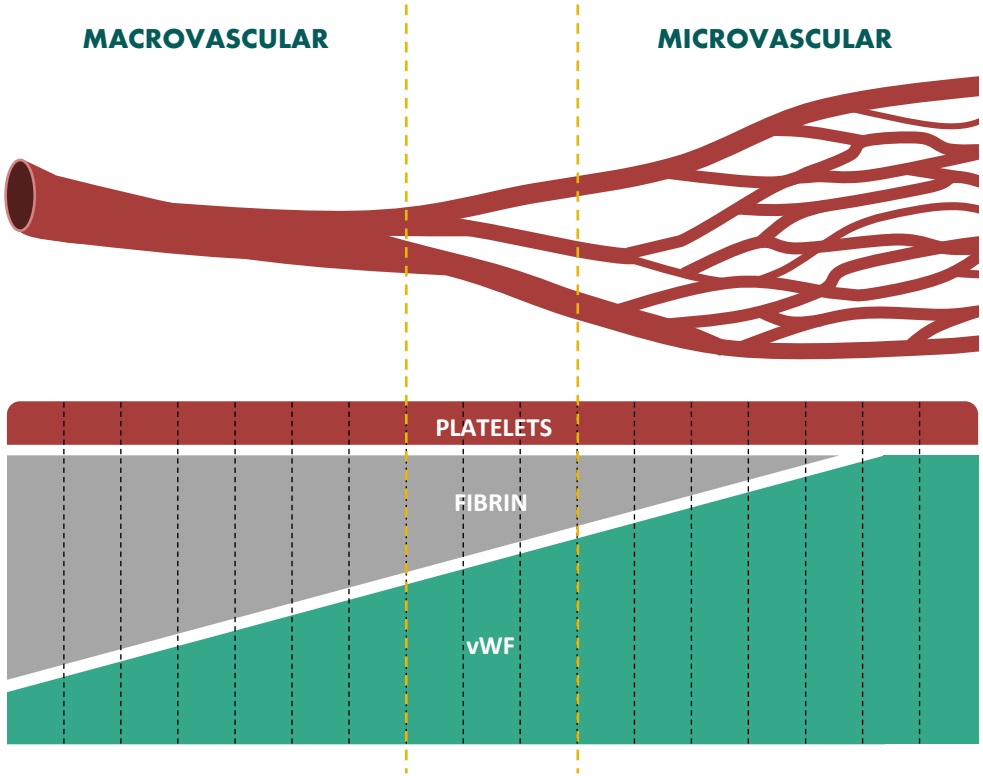
Current thrombolytic therapy (tPA) requires fibrin, limiting its efficacy



Moderately effective against
Macrovascular clots, as they also contain vWF

Ineffective against
Most microvascular clots, which generally lack fibrin

Microlyse targets both fibrin and vWF, making it applicable for any thrombotic indication, irrespective of the thrombus location and -composition



Effective against
Macrovascular clots with heterogeneous composition

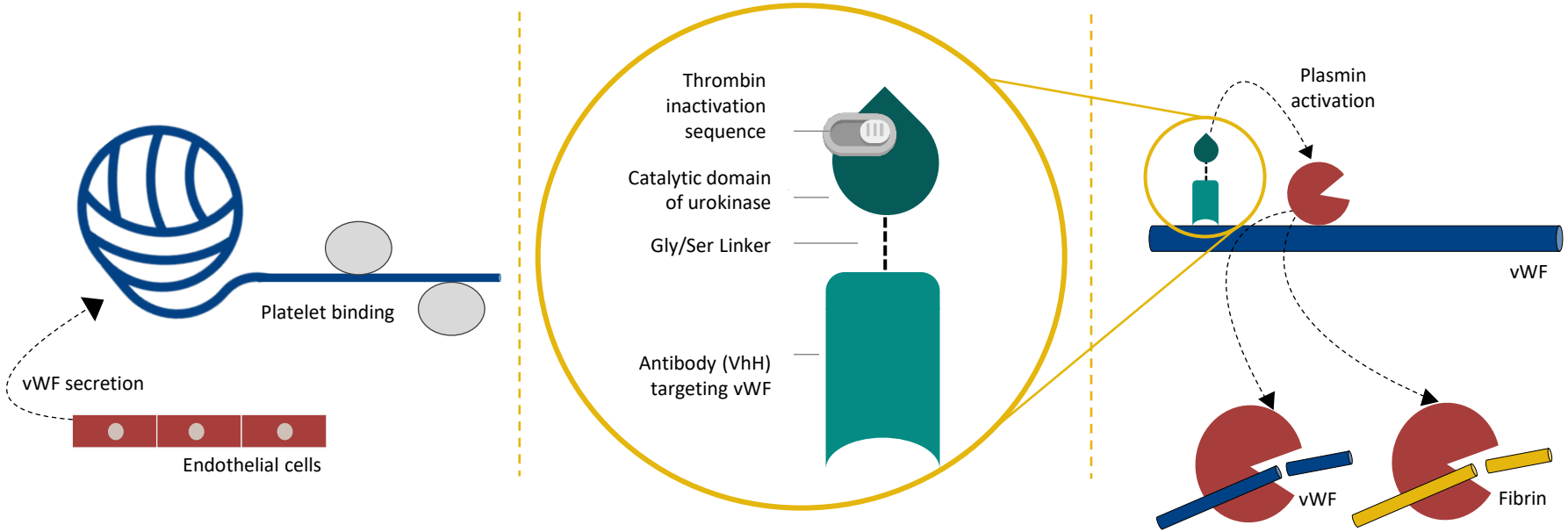
Effective against
Microvascular clots with high levels of vWF (without fibrin)

Microlyse is a single polypeptide that generates vWF-targeted plasmin activity

vWF is secreted by endothelial cells, then unrolls under flow and captures platelets

Microlyse has an antibody domain (VhH) that directs its catalytic domain towards vWF

After binding vWF, plasmin is activated which then degrades both vWF, but also fibrin if present



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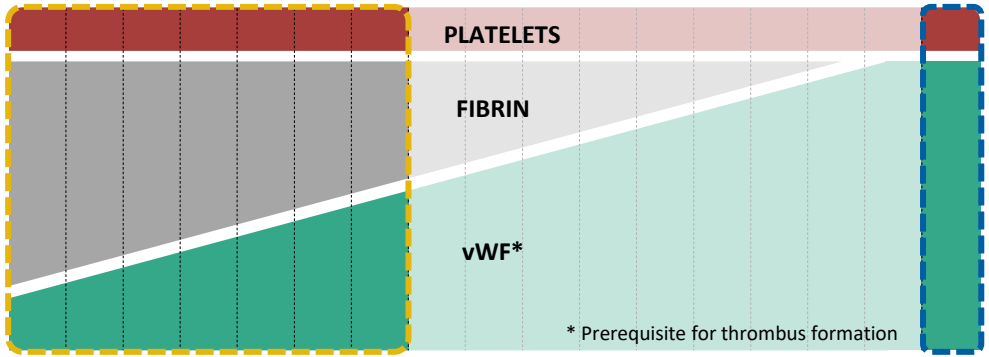
Microlyse is simultaneously being developed for aTTP, an orphan indication characterized by thrombi without fibrin, and acute ischemic stroke, the largest thrombotic indication characterized by heterogenous thrombi. Validating effectivity in both indications proves its applicability for any thrombotic indication.



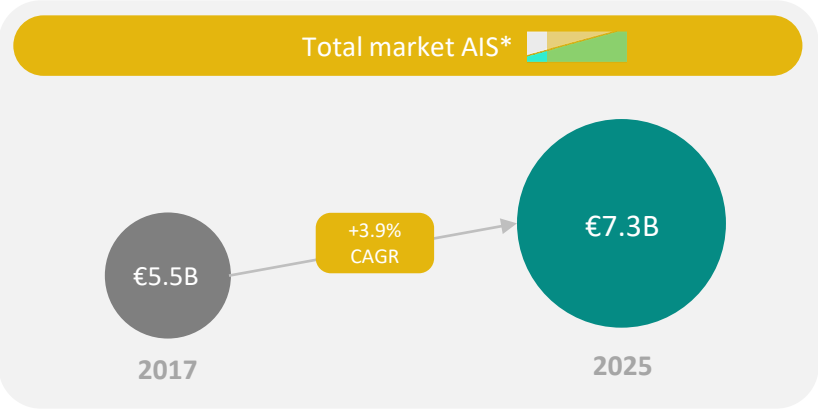
Acute Ischemic Stroke (AIS)

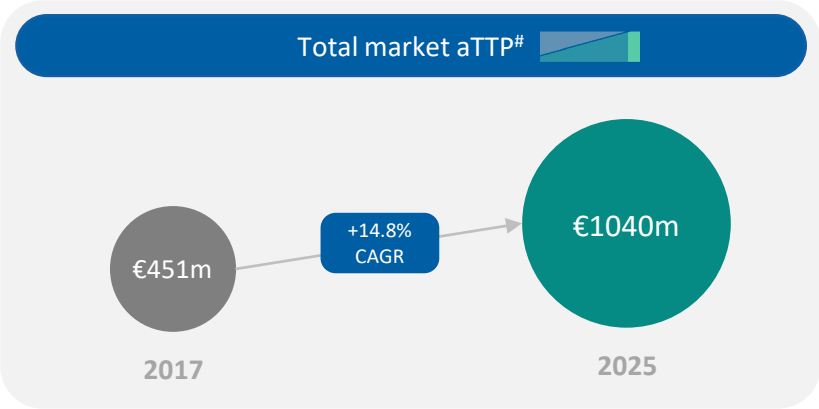
- Fibrin-rich
- vWF present

acquired TTP (aTTP)

- **No** fibrin
- vWF-rich

MARKET POTENTIAL





* Key metrics from 8MM, retrieved from GlobalData report GDHC171PIDR

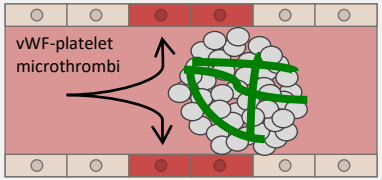
Accumulative sales proposals from immunosuppressants, Caplacizumab and Apadamtase-α

TARGED
TARGETED ENZYME DELIVERY

aTTP is an immune-disease, characterized by countless microthrombi that obstruct the blood flow towards various organs. Patients benefit from rapid revascularization, hence a shortened attack duration

EPISODE

SYMPTOMS
- Acute attacks
- Neurological, renal and gastro-intestinal symptoms



DIAGNOSIS

ER METHODOLOGY
- Low platelet counts
- Deficiency natural vWF cleaving enzyme (ADAMTS13)

EPIDEMIOLOGY
- **Incidence 7MM:** 7.500 episodes/year
- **Recurrence rate:** 80%
- **Mortality without SoC:** 90%

THERAPIES & UNMET NEEDS

IV COMBINATION THERAPY
- Plasma exchange (PEX)
- Immune suppression (IS)
- Caplacizumab: vWF-blocking nanobody

	PEX + IS	+ Caplacizumab
Mortality	~20%	~15%
Attack days	5	3-4
Plasma	40L (€100K)	30L

UNMET NEED
- **Shortened attack duration**

TARGED
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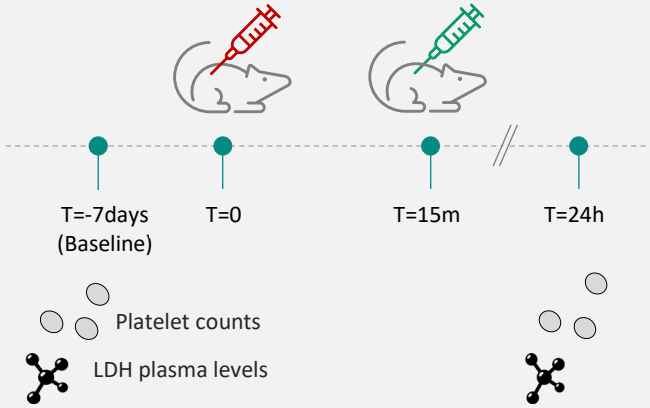
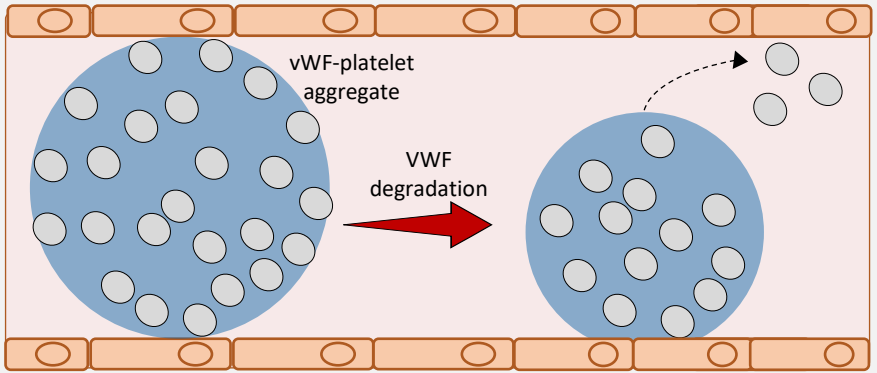
Microlyse was compared to Caplacizumab in a validated TTP mouse model. Hereto, platelet counts and LDH (biomarker for tissue damage) were investigated. Both are biomarkers for disease activity and severity in human clinical TTP studies with Caplacizumab

Therapies were given 15min after triggering TTP via administration of rhVWF to ADAMTS13$^{-/-}$ mice, and parameters were measured at baseline and after 24 hours

Hypothesis: by degrading vWF, Microlyse liberates platelets from microthrombi, reducing tissue damage as measured by LDH biomarker. These parameters were also assessed in Caplacizumab clinical trials



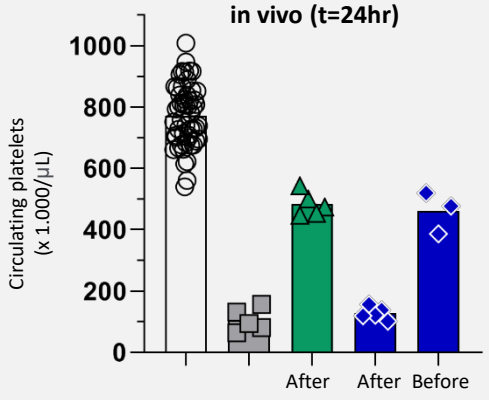


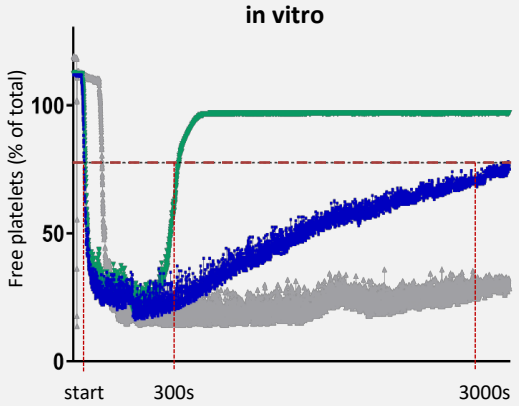
Microlyse degrades pre-existing microthrombi 10x faster than Caplacizumab, which explains a significant reduction in tissue damage

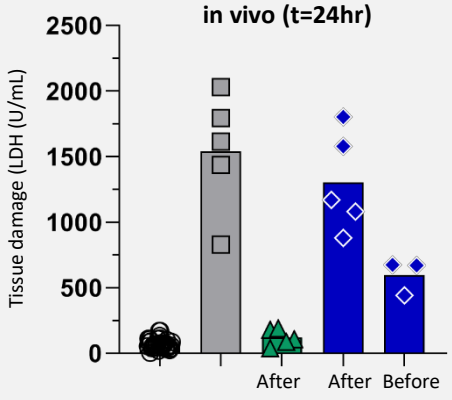
Microlyse effectively degrades pre-existing clots as seen in TTP attacks; Caplacizumab is more effective in preventing clot formation

At equimolar doses, Microlyse removes platelets from clots 10x faster than Caplacizumab

Resulting in a decreased ischemic period and, consequently, prevention of tissue damage







Baseline (t=0) | Saline | Microlyse (416nM) | Caplacizumab (416nM*)

* Caplacizumab is clinically administered at 60nM

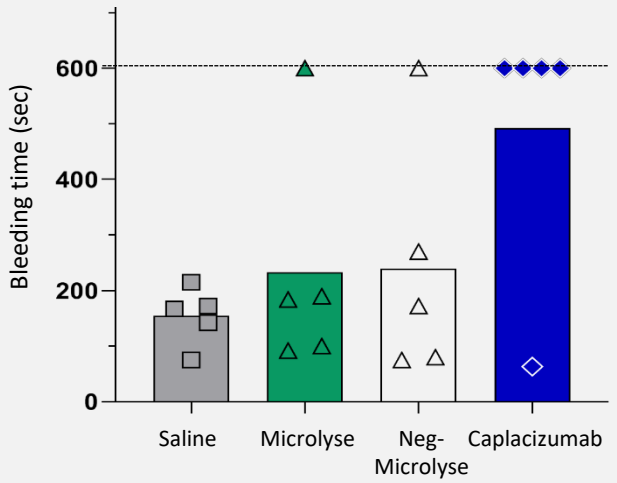
TARGED TARGETED ENZYME DELIVERY

BLEEDING & CLINICAL POTENTIAL

In additional mice, tail-cut was performed 15 minutes after treatment. Bleeding was assessed for max. 600 seconds. Microlyse did not affect bleeding time, indicating a superior bleeding profile when compared to Caplacizumab

Consequently, when compared to Caplacizumab, Microlyse holds the clinical potential to reduce attack duration and to limit tissue ischemia, yet without an increased bleeding tendency

BLEEDING *IN VIVO*



CLINICAL POTENTIAL

	PEX + IS	+ Caplacizumab	MIcrolyse
Mortality	~20%	~15%	<<
Attack days	5	3-4	<<
Plasma	40L (€100K)	30L	<<

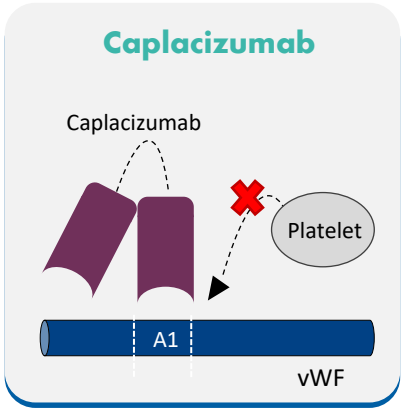
CAPLACIZUMAB RE-ADJUSTED CLINICAL GUIDELINES

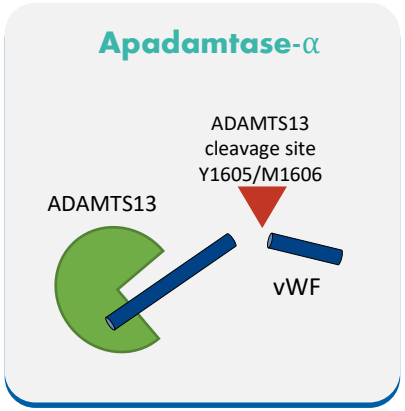
- ISTH 2020 Guidelines for TTP treatment:
  Cablivi is more suitable to prevent build-up than to accelerate breakdown
- ASH 2021 immune TTP consensus report
  Caplacizumab ”buys time”, allowing immunosuppressive therapy have ADAMTS13 levels recovered
- NICE rejects Cablivi for rare blood disorder TTP
  Cablivi is assumed to have no survival benefit in the long-term

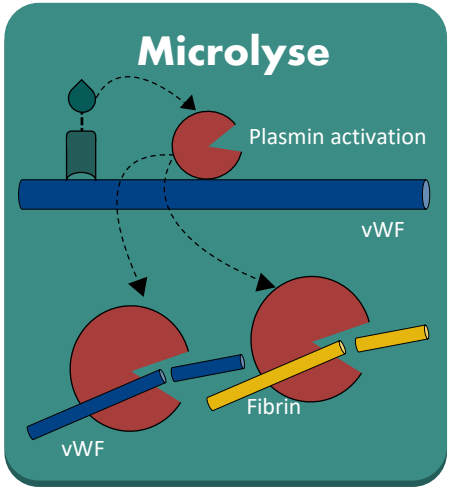
TARGED
TARGETED ENZYME DELIVERY

aTTP COMPETITION

Therapy	Company	Mechanism of action	Administration	Phase
Caplacizumab	Sanofi	Bi-head nanobody that blocks vWF (A1) and prevents platelet binding	Add-on to PEX	Market
Apadamtase-α	Takeda	ADAMTS13 surplus therapy to overcome auto-antibodies	Stand-alone/add-on	III
Microlyse	TargED	Active vWF cleavage via targeted plasmin activation	Stand-alone/add-on	Preclin.







TARGED
TARGETED ENZYME DELIVERY

Acute ischemic stroke (AIS) is the result of an occlusive thrombus, accounting for 90% of all stroke cases. Of these patients, only ~20% are eligible for intravenous treatment with rh-tPA and only ~5% are eligible for thrombectomy in addition

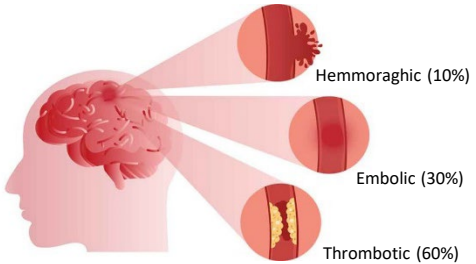
EPISODE

SYMPTOMS
- One side paralysis
- Sudden confusion
- Speech impairment
- Loss of vision / coordination
- Sudden, severe headache

EPIDEMIOLOGY
- **Incidence:** 15 million/year
- **Mortality:** 5 million/year
- **Permanently disabled:** 5 million/year

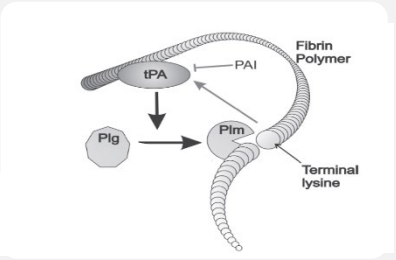
DIAGNOSIS

ER METHODOLOGY
- CT to differentiate occlusion from bleeding
- CT to determine location of blood clot



THERAPY

FIRST-IN-LINE: thrombolysis with rh-tPA (~20%)



ADDITIONAL: thrombectomy (~5%)

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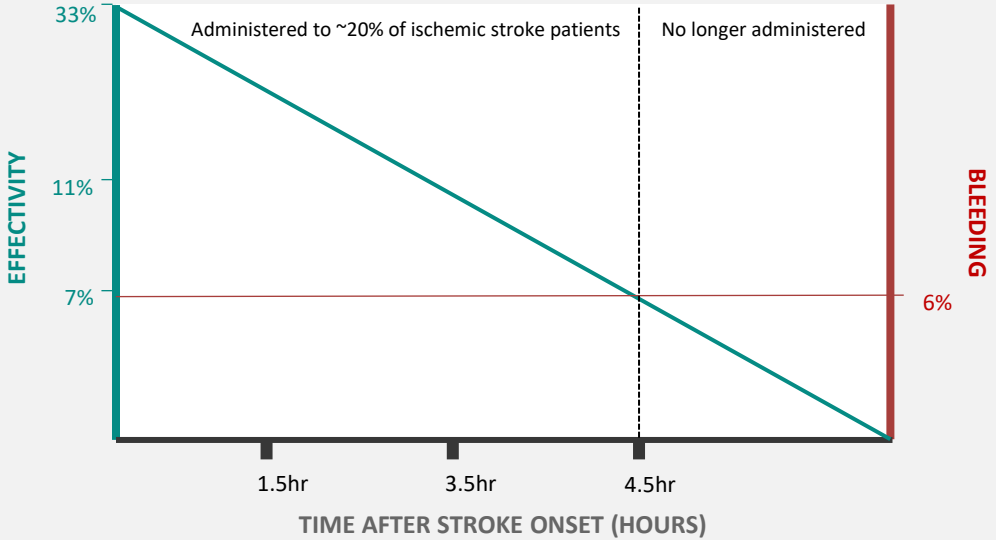
TARGETED ENZYME DELIVERY

tPA-resistance: a limited effectivity that decreases over time, with a persistent bleeding risk

Therapy with tPA has limited effectivity which decreases the later that tPA is administered after stroke symptom onset. Also, 6% of patients treated with tPA result in therapy-related bleeding. Together, this results in a 4.5 hours therapeutic window

As unmet clinical needs, KOLs emphasize the absence of therapy for ~80% of existing AIS patients, the need for more effective therapy, faster clot breakdown, and a decreased bleeding risk



UNMET CLINICAL NEEDS

LIMITATIONS OF tPA

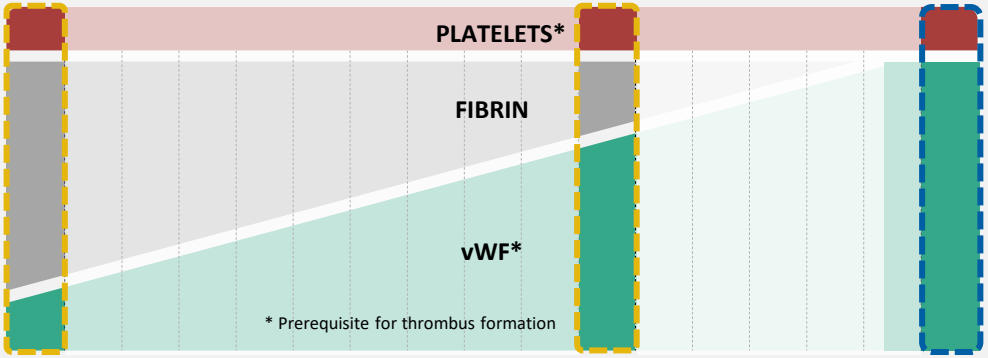
Time after onset	Therapeutic response
0 - 1.5 hr	33%
1.5 - 3 hr	11%
3 – 4.5 hr	7%
>4.5 hr	Outweighed by bleeding risk

UNMET NEEDS

- **Therapy for ~80% of untreated AIS patients**
- **Faster clot breakdown, decreasing:**
  Brain damage, permanent disability, mortality
- **Reduced bleeding risk**

TARGED
TARGETED ENZYME DELIVERY

Microlyse was compared against tPA in a **tPA-sensitive** (thrombin-induced), as well as in a **tPA-resistant** ($FeCl_3$-induced) stroke model



AIS – Thrombin model (Oset, 2007)

- Fibrin-rich
- vWF present
- **tPA SENSITIVE**

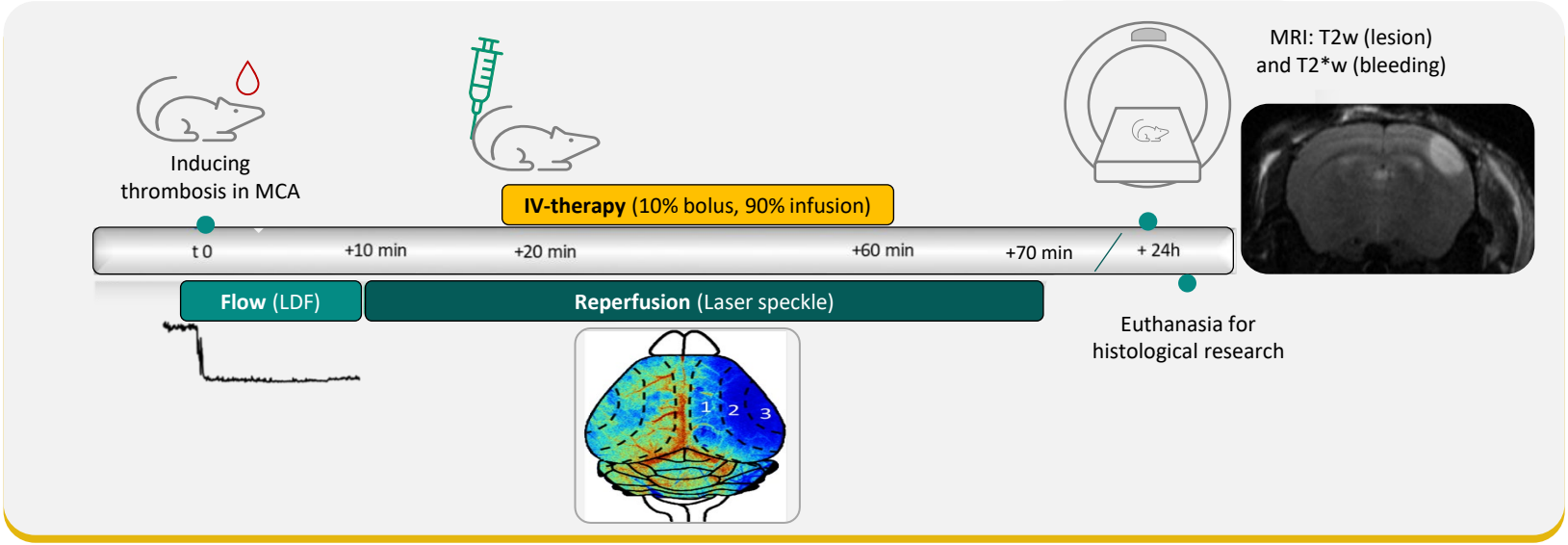
AIS – $FeCl_3$ model (Karatas, 2011)

- Low fibrin
- vWF-rich
- **tPA RESISTANT**

acquired TTP (aTTP)

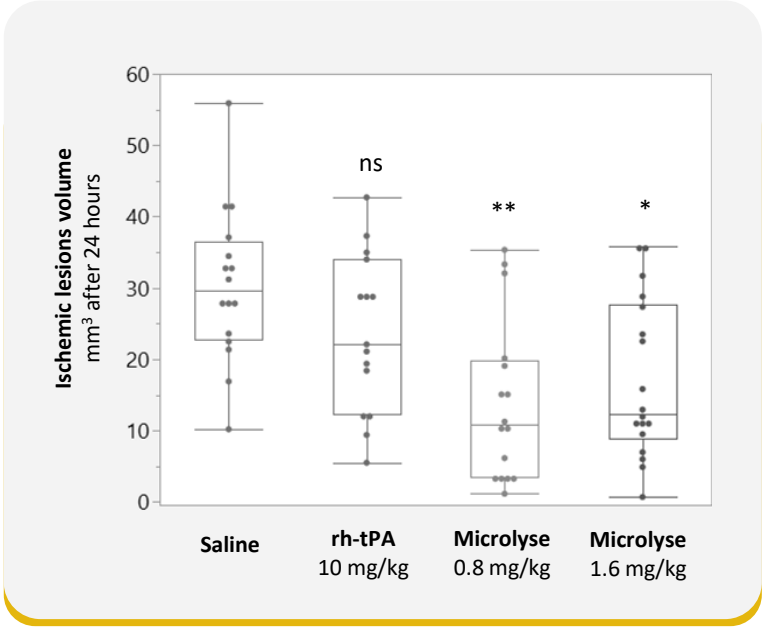
- **No** fibrin
- vWF-rich

tPA-resistant stroke was induced in the middle cerebral artery (MCA) via topical application of $FeCl_3$. Outcome parameters included lesion and bleeding after 24 hours



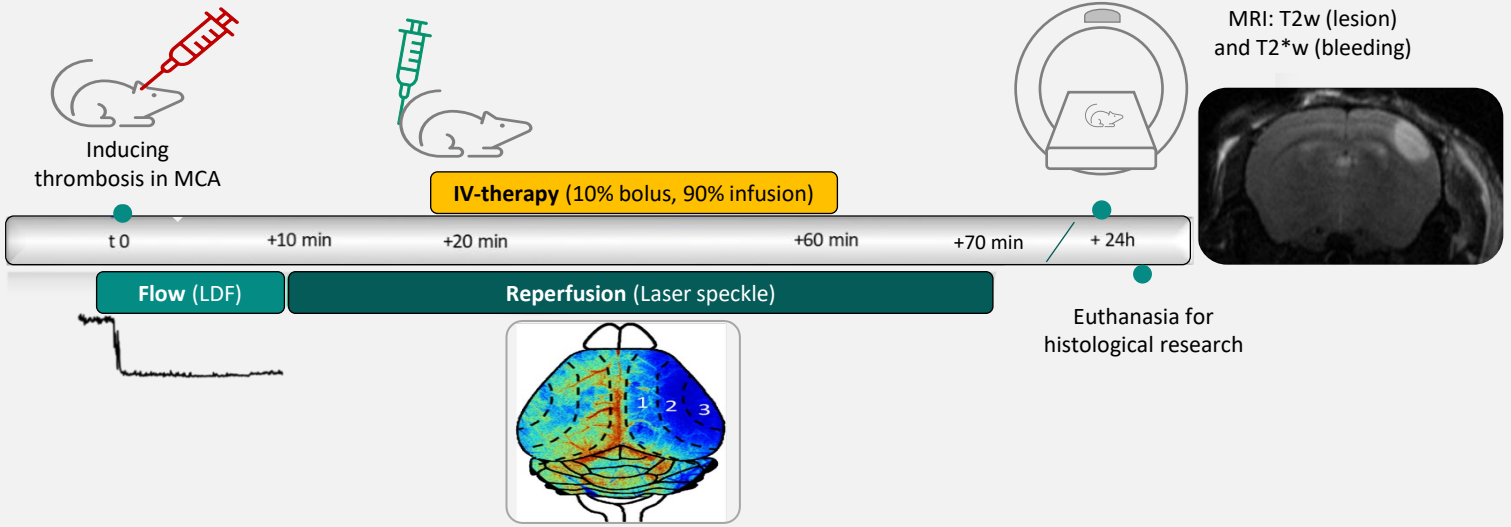
TARGED TARGETED ENZYME DELIVERY

In a **tPA-resistant ($FeCl_3$-induced) AIS model** Microlyse shows superiority in reducing lesion volume after 24 hours as compared to tPA

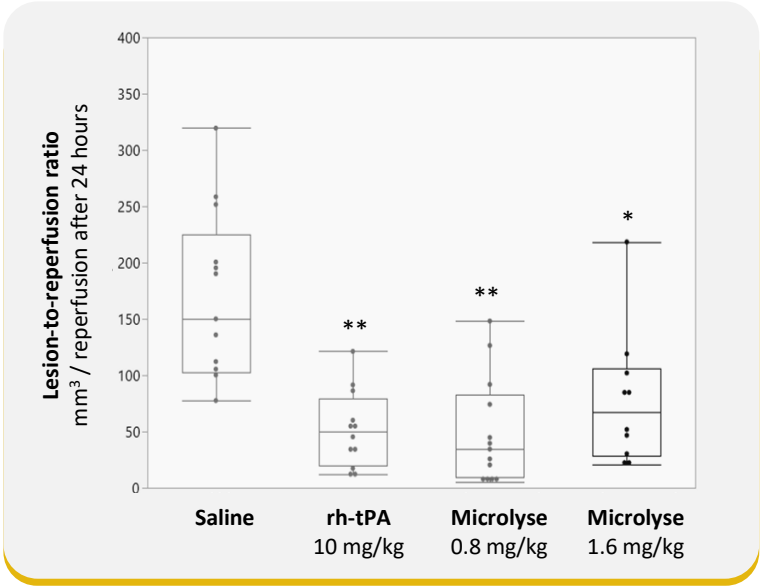


Boxes show median and quartiles. Whiskers show min and max. Individual values are plotted. Line indicates the mean. Wilcoxon test after Kruskal-Wallis Test.

tPA-sensitive stroke was induced in the middle cerebral artery (MCA) via IV-thrombin. Outcome parameters included reperfusion within 70 minutes and both lesion and bleeding after 24 hours



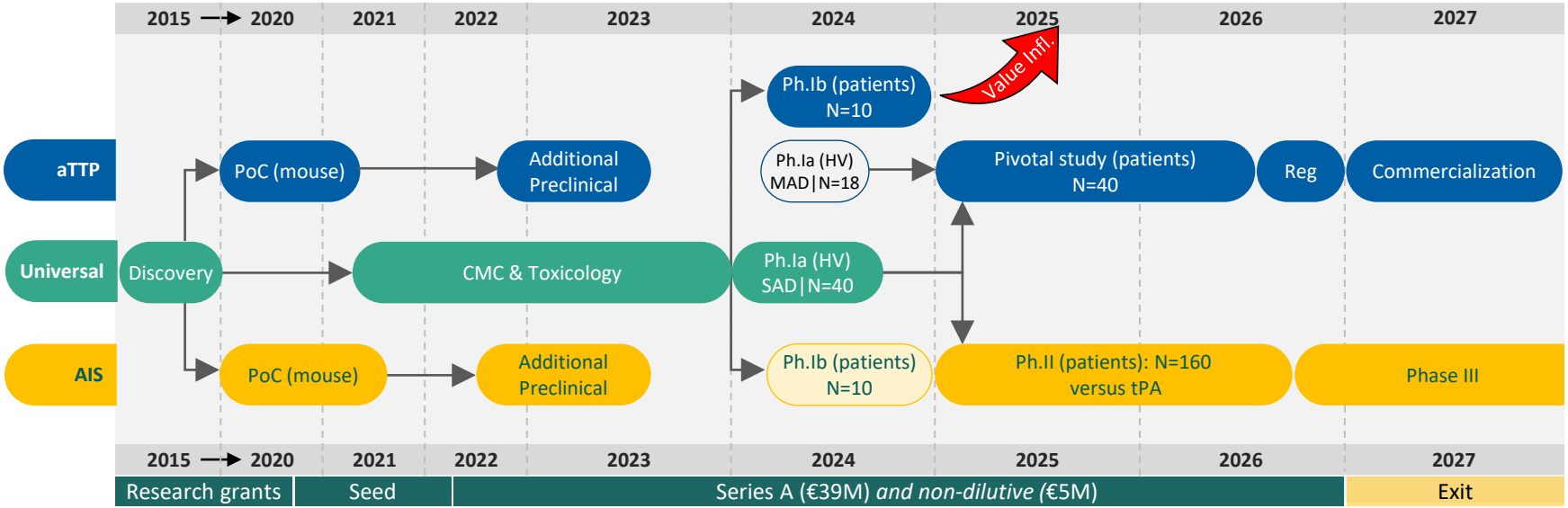
In a **tPA-sensitive (thrombin-induced) AIS model** Microlyse shows non-inferiority as compared to tPA



Boxes show median and quartiles. Whiskers show min and max. Individual values are plotted. Line indicates the mean. Wilcoxon test after Kruskal-Wallis Test.

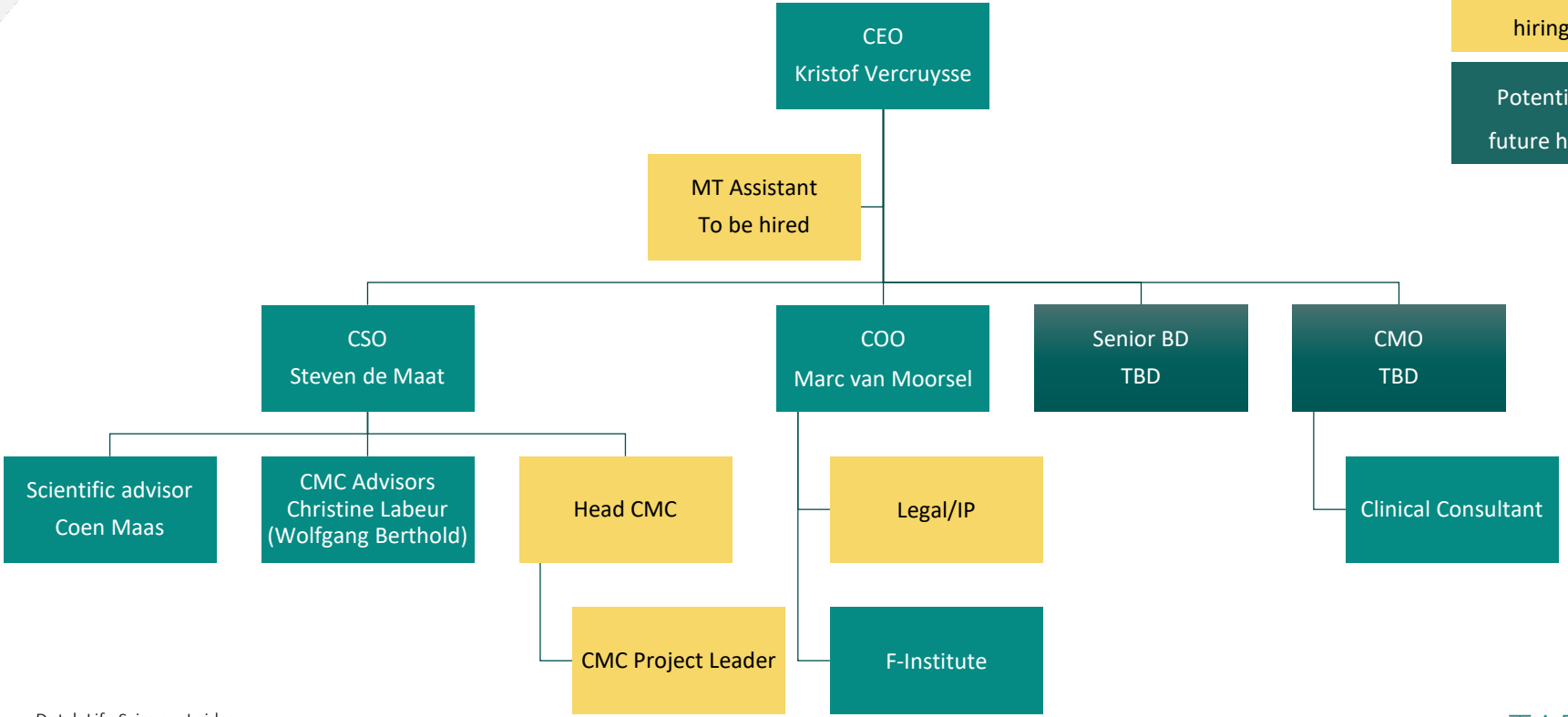
SINGLE PHASE-I FOR ALL THROMBOTIC INDICATIONS

With the Series A investment, TargED will perform (1) stroke studies in larger species (addressing both efficacy and therapy-related bleeding), (2) IND enabling studies, (3) phase-I in healthy volunteers including patient cohorts, (4) pivotal study in aTTP patients and (5) a phase II study in AIS patients



TARGED
TARGETED ENZYME DELIVERY

ORGANIZATION TO DATE



ADVISORS aTTP

	**Prof. Karen Vanhoorelbeke** Leuven, Belgium	**Head of Laboratory of Thrombosis research, 161 publications** Topic: Molecular mechanisms by which the hemostatic proteins vonWillebrand factor (vWF) and its cleaving enzyme ADAMTS13 contribute to health and disease
	**Prof. Paul Knoebl** Vienna, Austria	**Scientific expert in TTP, 170 publications.** Topic: Immune mediated coagulation disorders, Thrombotic microangiopathy (incl. TTP), Critical illness coagulopathy, rare bleeding disorders.
	**Prof. Spero Cataland** Ohio, USA	**Hematologist with a focus on non-malignant blood disorders, 160 publications.** Topic: Thrombotic microangiopathy including TTP and aHUS. Clinical experience with Caplacizumab for acquired TTP and Recombinant ADAMTS13 for congenital TTP
	**Dr. Katerina Pavenski** Toronto, CND	**Head of the Division of Transfusion Medicine, clinical hematologist** Topic: clinical transfusion medicine, patient blood management, therapeutic apheresis, and TTP/cm-HUS. Clinical experience with Caplacizumab.
	**Prof. Flora Peyvandi** Milan, ITA	**Professor of Internal Medicine at the University of Milan, over 500 publications** Topic: rare bleeding disorders. Principal investigator in TITAN and HERCULES Caplacizumab trials. President of ISTH 2020.

ADVISORS STROKE

 **Prof. Johannes Boltze** Warwick, UK	**Full professor of Neuroscience, and editorial board member of multiple scientific journals, including Stroke, PLoS One, Cell Transplantation and Translational Stroke Research, over 175 publications.** Topic: Brain ischemia, preclinical animal models, translational models in stroke
 **Prof. Rick Dijkhuizen** Utrecht, Netherlands	**Head of Biomedical MR Imaging and Spectroscopy Group, over 200 publications** Topic: MR Imaging in preclinical stroke models. Expert in Pre-clinical models in AIS and Principal Investigator in Collaboration for New Treatments for Acute Stroke
 **Prof. Jeffrey Saver** Los Angeles, USA	**Head of UCLA Stroke Center, more than 700 publications and book chapters.** Topic: Stroke prevention, acute stroke treatment, stroke diagnosis, and cognitive and behavioral consequences of stroke. Actively participating and designing multiple clinical trials.
 **Prof. Diederik Dippel** Rotterdam, Netherlands	**Neurologist with interest in Vascular and acute neurology, over 300 publications on stroke** Topic: PI of several investigator-driven multicenter randomized clinical trials for treatment of acute ischemic stroke. Research Leader of Collaboration for New Treatments for Acute Stroke
 **Prof. Werner Hacke** Heidelberg, Germany	**Senior Professorship of Neurology at the University of Heidelberg, Germany; more than 500 publications** Past-President of the German Neurological Society, the founding President of the European Stroke Organization (ESO), and a Past President of the World Stroke Organization 2016-2018.
 **Prof. Bart van der Worp** Utrecht, Netherlands	**Neurologist and previous President of European Stroke Organization (ESO), over 250 publications** Topic: cerebrovascular diseases. (co-)Chief Investigator of the randomized clinical trials HAMLET, PAIS, COOLIST, VAST, PRECIOUS, APACHE-AF and MR ASAP.

OUR ULTIMATE GOAL IS TO DELIVER EFFECTIVE AND SAFE THROMBOLYSIS

- Microlyse: effective thrombolysis for various forms of thrombosis
- Preclinically validated in two thrombotic indications
  - Acquired Thrombotic Thrombocytopenic Purpura (aTTP; orphan indication);
  - Acute ischemic stroke (AIS)
- Worldwide, exclusive license on IP, covering Microlyse and variant fusion proteins
- February 22nd, 2022: €39 million Series A investment
- Deliverables (end 2026):

1. **Acute ischemic stroke:** POC data in large animal species, including bleeding and functional outcome (2023)
2. **Independent of indication:** full CMC (non-GMP and GMP) and toxicology program (end 2023)
3. **Independent of indication:** Phase I study in healthy volunteers, including preliminary POC in patients (2024)
4. **Acquired Thrombotic Thrombocytopenic Purpura (aTTP):** successful completion of Pivotal study (early 2026)
5. **Acute Ischemic stroke:** successful completion of phase II POC study (end 2026)

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TARGETED ENZYME DELIVERY