Silence Therapeutics

Collaboration with Mallinckrodt Pharmaceuticals in Complement-mediated Diseases

July 2019

Agenda

• Opening remarks	Dr David Horn Solomon, Chief Executive Officer
• Collaboration with Mercedes	Dr David Horn Solomon, Chief Executive Officer
• R&D Update	Dr Giles Campion, Head R&D, Chief Medical Officer
• Q&A	All participants

David Horn Solomon
CEO

Giles Campion
Head R&D, CMO

Rob Quinn
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John Strafford
Head BD

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Collaboration with Mallinckrodt Pharmaceuticals for Complement-Mediated Diseases

- Agreement provides Mallinckrodt with exclusive worldwide licence for Silence's C3 complement asset (SLN500), with options to licence up to two additional complement-targeted assets
- Silence will be responsible for development of each asset until the end of Phase 1, after which Mallinckrodt will take over clinical development and responsibility for commercialisation
- This deal provides further validation for Silence's proprietary siRNA platform, strengthening our position as a leader in RNA interference therapeutics

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Mallinckrodt Pharmaceuticals

Summary of Terms

$20 million Upfront

Up to **$10 million** in research milestones for SLN500 and each optioned asset, in addition to funding for Phase 1 clinical development, including GMP manufacturing

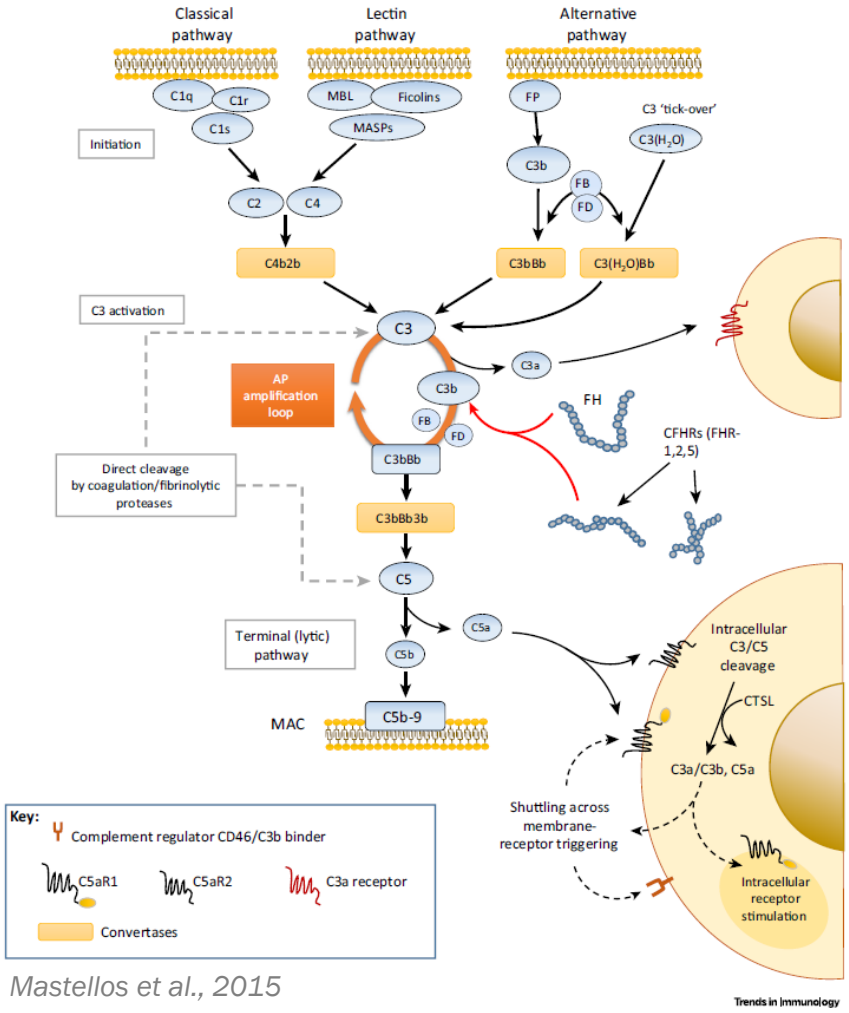
Potential clinical and regulatory milestones of up to **$100 million** for SLN500, as well as commercial milestones of up to **$563 million**. Up to **$703 million** in clinical, regulatory and commercial milestones per additional asset, should Mallinckrodt exercise its option

Tiered low double-digit to high-teen royalties on net sales

Equity investment of **$5 million,** non-executive Director seat on Silence Board to be filled by **Steven Romano, M.D.**, Mallinckrodt Chief Scientific Officer

GalNac siRNAs for the Treatment of Complement-mediated Diseases

Schematic overview - complement system



Mastellos et al., 2015

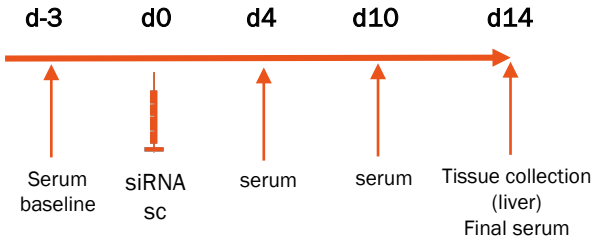
Targeting the complement system offers a broad indication spectrum (such as Paroxysmal Nocturnal Hemoglobinuria, Myasthenia gravis, C3 Glomerulopathy, atypical Hemolytic Uremic Syndrome or Cold Agglutinin Disease)

- **The Complement system** is part of the innate immune system and consists of 3 pathways
- > 30 serum proteins (many made in hepatocytes)
- It represents an activation cascade with various effector functions, such as MAC (membrane attack complex) formation for pathogen destruction and activation of immune cells
- First drug on the market targeting the complement pathway is Eculizumab (Soliris, C5 Ab)
- **There is unmet need** because Eculizumab is not consistently effective for all patients (mutations, non responders) and indications

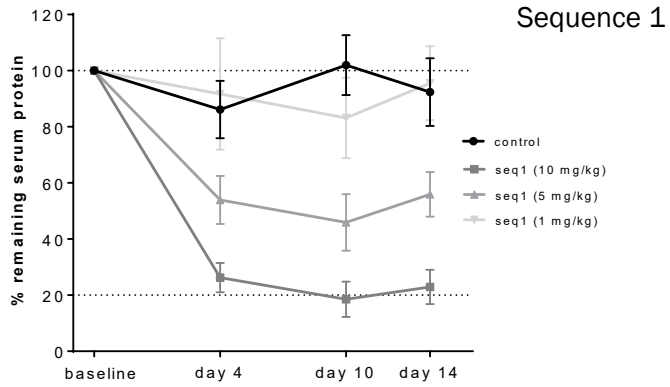
SLN500 - Proof of Mechanism In Vivo

> **Study design:**

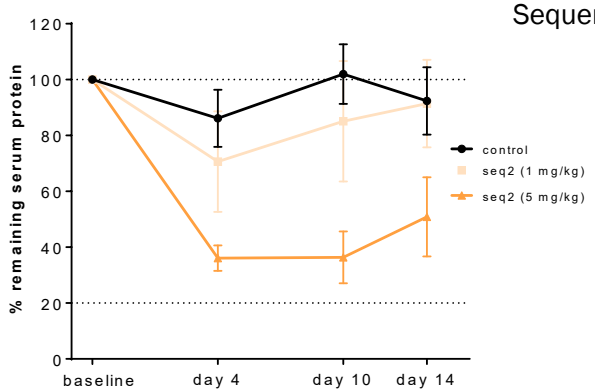
- n=4 healthy mice per group, serum sampling at day -3, 4, 10 and 14, liver tissue at day 14
- siRNAs: **non-optimized** GalNac conjugated chemistry



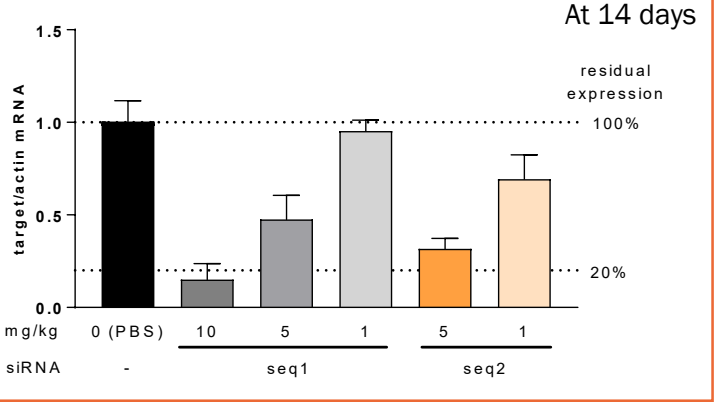
C3 SERUM PROTEIN



C3 SERUM PROTEIN



C3 RNA



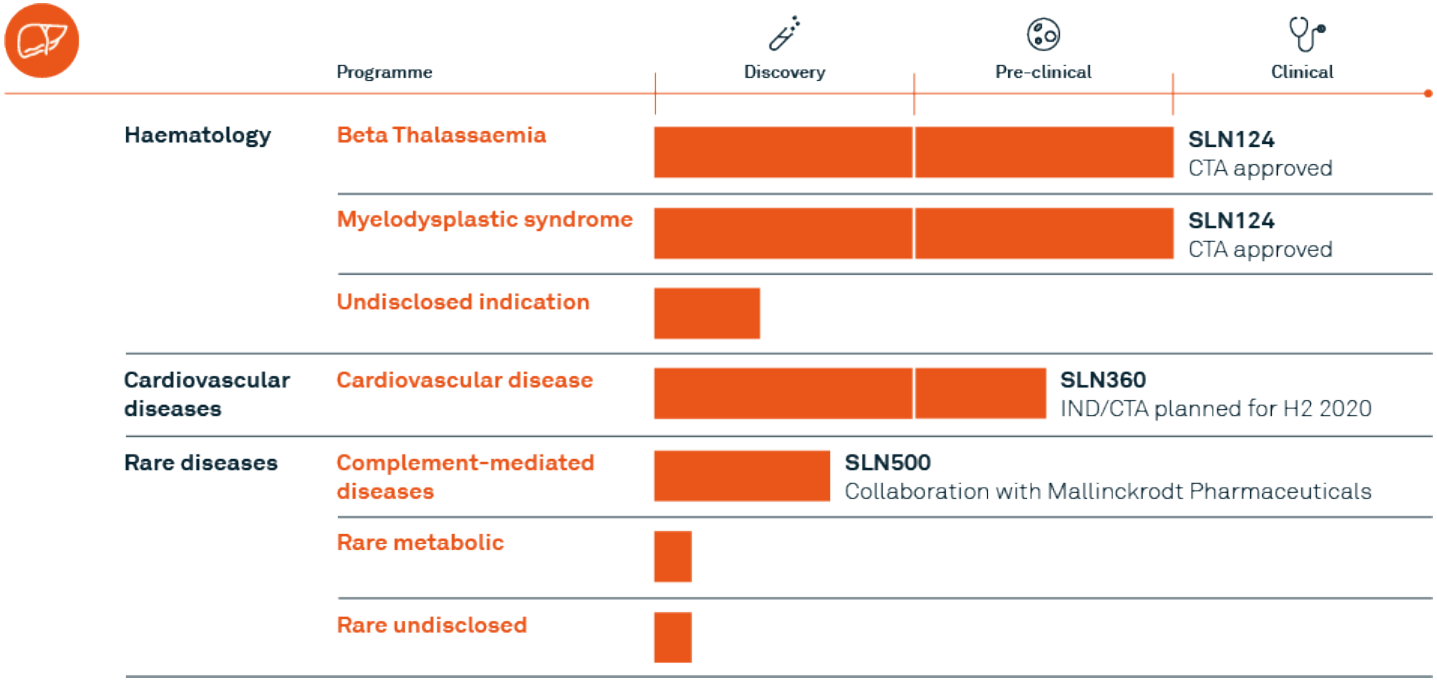
C3 knock down:
> 80 % mRNA & protein knock down achieved using non-optimized siRNAs

→ Identification of 2 potent siRNA sequences for lead optimization and NHP studies (using advanced chemistry)

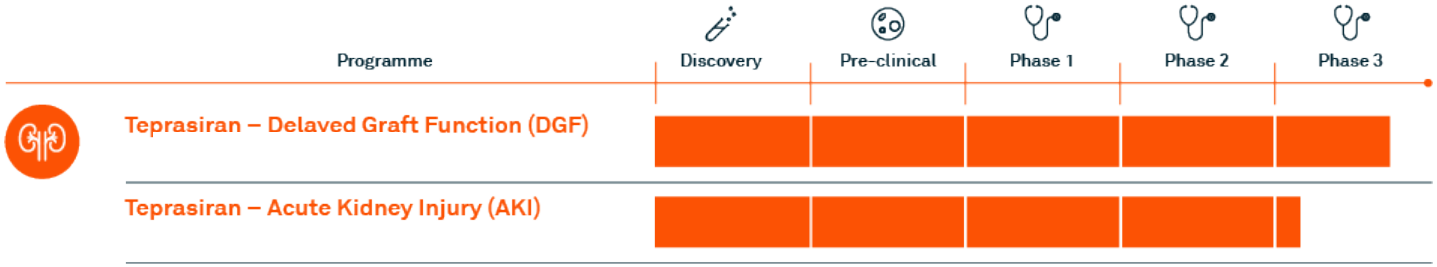
Other Recent Highlights

- Clinical Trial Application approved for SLN124 in April 2019 with MHRA
  - First patients expected to enter a Phase Ib study in H2 2019
  - Granted Orphan Drug Designation by the European Medicines Agency for the treatment of β-Thalassemia
- SLN360, an Lp(a) targeting siRNA for cardiovascular disease advanced and has started IND-Enabling studies in Feb 2019
- Out-licenced programme, QPI-1002, for Prevention of Acute Kidney Injury progressed to Phase III clinical trial by partner Quark Pharmaceuticals, Inc.
- New leadership in place with the recruitment of Dr David Horn Solomon, an experienced public company biotech CEO and board member as Chief Executive Officer. Dr Giles Campion joins as Head R&D and Chief Medical Officer
- Settlement and License Agreement with Alnylam Pharmaceuticals for tiered royalty on net sales of ONPATTRO™ in the EU

Our pipeline



Out-Licensed Technology to Quark Pharmaceuticals

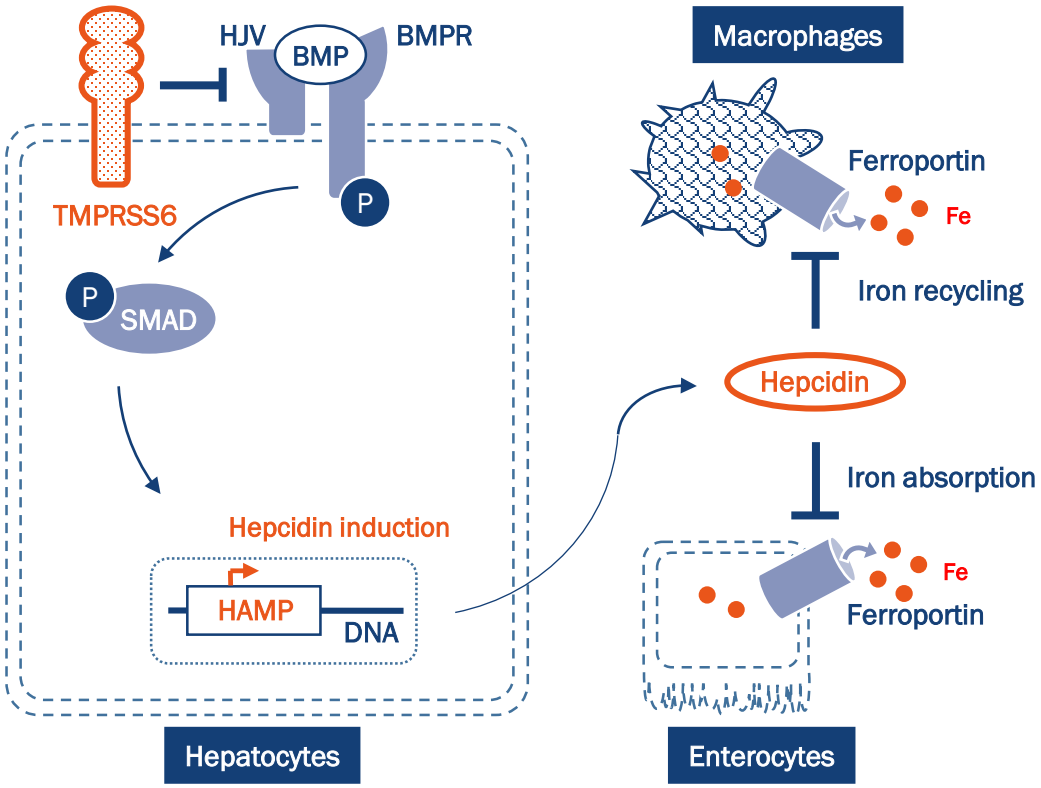


SLN124

for the treatment of

Iron Overload Disorders

SLN124 Mechanism of Action: Increasing Hepcidin by Silencing its Repressor TMPRSS6



- **TMPRSS6** (Transmembrane Protease, Serine 6) is a negative regulator of the BMP/SMAD signaling pathway
- Inhibition of TMPRSS6 in hepatocytes induces Hepcidin expression
- Hepcidin reduces absorption of dietary iron and the release of iron from cellular storage, thereby reducing circulatory iron levels
- The liver is the predominant source of Hepcidin

Silencing TMPRSS6

1. Increases Hepcidin levels
2. Reduces iron levels
3. Improves erythropoiesis
4. Reduces anemia & iron overload

We are Planning to Initiate a Multicentre, Randomised, Placebo Controlled Phase 1b in 2019

This is a two part first-in-human, multicenter, randomized placebo controlled single ascending and multiple dose study to assess the preliminary safety, tolerability, PK and efficacy of SLN124 administered subcutaneously for the treatment of non-transfusion dependent thalassemia and low risk myelodysplastic syndrome.

Study design

> Part A:

- Single dose escalation study to evaluate the dose response to SLN124 with a view to identify the most appropriate dose to bring forward into the multiple dose portion of the study
- Primary aim to determine the safety and tolerability of SLN124 for the treatment of non-transfusion dependent β-thalassemia

> Part B:

- Bring forward the most efficacious and best tolerated dose to evaluate multiple administrations of SLN124 on hematinic parameters in patients with β-thalassemia and MDS
- Primary aim to determine the safety and tolerability of multiple doses of SLN124 for the treatment of non-transfusion dependent β-thalassemia and low risk myelodysplastic syndrome

SLN360

for the treatment of

Cardiovascular disease with high Lp(a)

SLN360 targets Lp(a) - an Independent Risk Factor for CVD

Lp(a) levels are genetically determined

Recognised as a major untreated risk factor in cardiovascular disease

Lp(a) levels are not significantly modifiable through diet or approved pharmacological therapies

Large population worldwide with up to 10% with >80mg/dL (2x increased MI risk)

Multiple mechanisms by which Lp(a) causes CVD

- > Pro-atherogenic
- > Pro-thrombotic
- > Pro-inflammatory

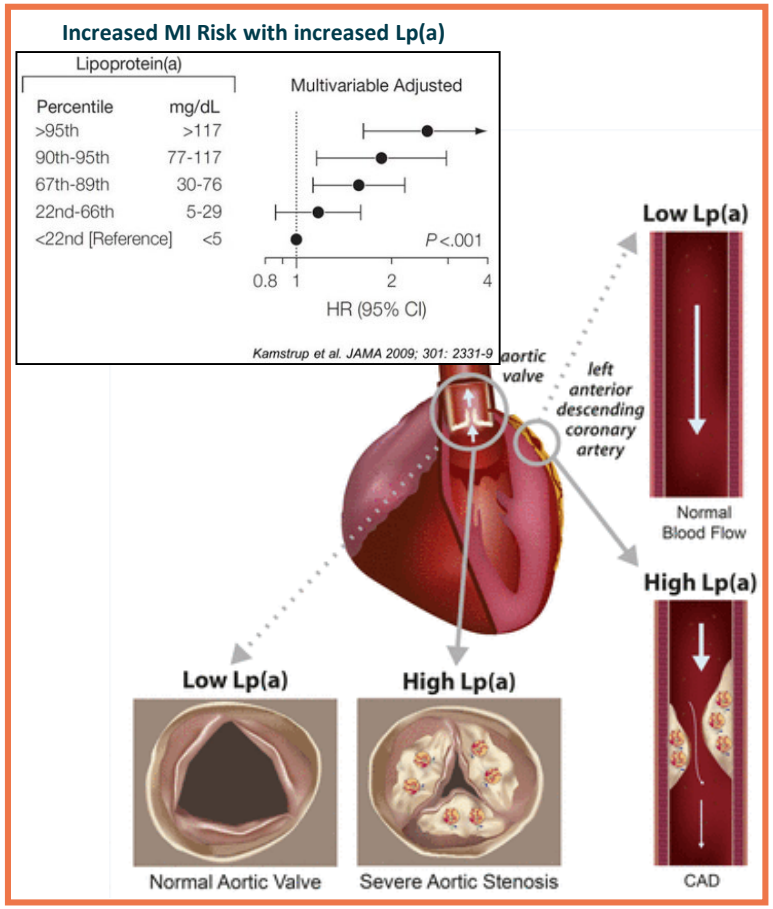
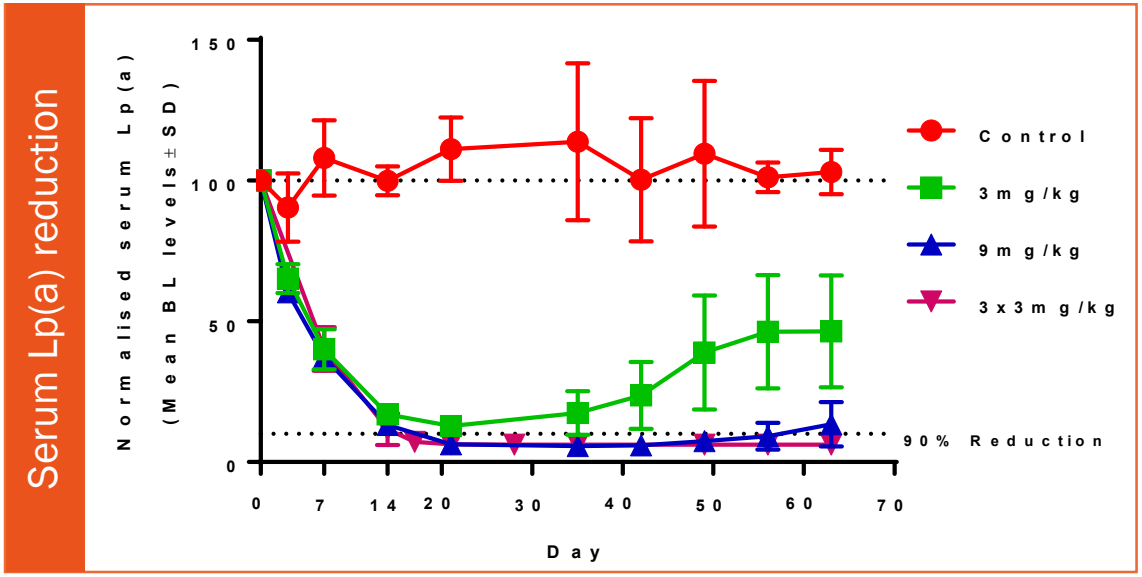
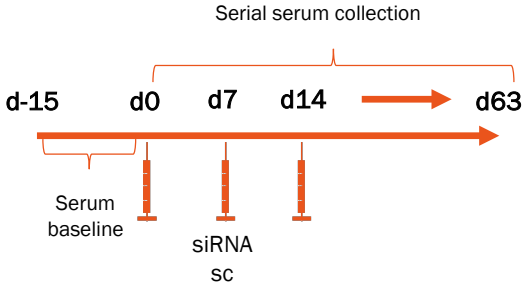


Image obtained from the Journal of Lipid Research March 2016

Targeting Lp(a) with SLN360 has the potential to address major unmet needs in cardiovascular disease

Proof of mechanism achieved





Group	mg/kg	Days
1	0	0
2	3	1
3	9	1
4	3	1, 7, 14

Prolonged serum knockdown of Lp(a)

> Multiple dosing at 3mg/kg resulted in sustained reduction of Lp(a) serum levels (>90%) for at least over two months after first dose (max ~>95% KD)

> Similar outcome after single subcutaneous injection of SLN360 at 9mg/kg.

> Over 85% KD at NADIR for single 3mg/kg injection with 50% KD still observed after 2 months post treatment

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Q&A