Spark Therapeutics, Inc.

Corporate Overview
November 2018

Forward-looking statements

This presentation contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, including statements regarding the company's product candidates, including LUXTURNA™ (voretigene neparvovec-rzyl), *SPK-7001*, *SPK-9001, SPK-3006,* and *SPK-8011*. The words ‘‘anticipate,’’ ‘‘believe,’’ ‘‘expect,’’ ‘‘intend,’’ ‘‘may,’’ ‘‘plan,’’ ‘‘predict,’’ ‘‘will,’’ ‘‘would,’’ ‘‘could,’’ ‘‘should,’’ ‘‘continue’’ and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements are based on management's current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in, or implied by, such forward-looking statements. These risks and uncertainties include, but are not limited to, the risk that: (i) voretigene neparvovec may not be approved in any markets outside of the U.S.; (ii) the improvements in functional vision demonstrated by LUXTURNA in our clinical trials may not be sustained over extended periods of time; (iii) we may not achieve our expected objectives for commercialization for LUXTURNA; (iv) we may be unable to maintain or continue to enter into agreements with payers for the provision of LUXTURNA; (v) if approved, Novartis may not be successful in commercializing or selling voretigene neparvovec in one or more markets; (vi) we may not receive any additional milestone or royalty payments from Novartis, Pfizer or our other collaborators; (vii) our early preliminary clinical results for our product candidate, *SPK-8011*, for hemophilia A may not be sustained; (viii) our implementation of a prophylactic approach to steroid administration for subjects participating in our *SPK-8011* clinical trials may not prevent an immune response; (ix) we may not be successful in initiating a multinational Phase 3 clinical trial for *SPK-8011* and the timing and design of such trial may vary from our expectations; (x) our initial evaluation of safety in non-inhibitor patients for *SPK-8016* may not be successful; (xi) interim data from our *SPK-7001* Phase 1/2 clinical trial, including data to be generated from our recently expanded cohort, may not support further development of this product candidate; (xii) we may not advance our *SPK-3006* program into the clinic when anticipated, or at all; (xiii) the data for *SPK-3006* IND-enabling studies may not be sustained; (xiv) our preliminary results of scale-up to non-human primates supporting the initiation of clinical studies of *SPK-3006* in humans may not be sustained; (xv) there are comparability issues for *SPK-8011* resulting from changes in our adherent manufacturing process to a suspension cell culture manufacturing process; and (xvi) any one or more of our product candidates in preclinical or clinical development will not successfully be developed and commercialized. For a discussion of other risks and uncertainties, and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the "Risk Factors" section, as well as discussions of potential risks, uncertainties and other important factors, in our Annual Report on Form 10-K, our Quarterly Reports on Form 10-Q and other filings we make with the Securities and Exchange Commission. All information in this presentation is as of the date of the presentation, and Spark undertakes no duty to update this information unless required by law.

Spark is a fully integrated, commercial gene therapy platform company seeking to challenge the inevitability of genetic disease

- **LUXTURNA** is the **first approved gene therapy** for a genetic disease in the US
  - **US launch underway; ex-US rights** licensed to **Novartis Pharmaceuticals** with **EC action** expected **4Q18**
- **Initiating Phase 3** run-in study in **hemophilia A by YE18**
  - Preliminary **Phase 1/2 data support** emerging **safety, efficacy and durability** profile of *SPK-8011*
  - **Enrolling additional participants** in Phase 1/2 study utilizing **suspension material** and **prophylactic steroids**
  - ***SPK-8016*** for hemophilia A **inhibitor market: IND cleared** and, per FDA agreement, initially evaluating **safety** in **non-inhibitor patients**
- ***SPK-3006*** for **Pompe** disease: **GLP toxicology** and biodistribution study **ongoing,** targeting initiation of **Phase 1/2** trial in **2019**
- A **fully integrated** adeno-associated virus **(AAV) gene therapy platform** and **pipeline** of clinical and preclinical candidates across multiple target tissues:
  - **Only FDA-licensed AAV commercial manufacturing facility; scaled suspension** and **adherent capabilities**
  - **Fidanacogene elaparvovec** for **hemophilia B: Progressed** by **Pfizer** into **Phase 3**
  - **Follow-up ongoing** for ***SPK-7001*** Phase 1/2 trial in **choroideremia**
- **$671.4 million** in cash and equivalents at 9/30/18

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LUXTURNA (voretigene neparvovec-rzyl): US launch underway

LUXTURNA is the first FDA-approved gene therapy for a genetic disease: US launch underway

FDA-approved labeling for LUXTURNA

- Provides **genetic indication** without regard to phenotypic diagnosis
- **No** FDA-imposed **upper age limit**
- Eligibility of appropriate patients with the indicated genetic diagnosis is left to the **clinical judgment of the treating physician**
- Clearly described **safety profile**

Durable efficacy demonstrated up to three years, with follow-up ongoing

LUXTURNA™
voretigene neparvovec-rzyl
for subretinal injection

Ex-US rights licensed to Novartis Pharmaceuticals*

CHMP positive opinion received for LUXTURNA in September; EC action expected as soon as this month

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*Terms include $105MM upfront, an additional $25MM on EMA approval, up to an aggregate $40MM on initial sales in certain ex-US markets and a flat mid-twenties percent royalty on net sales.

LUXTURNA U.S. launch drivers and enablers

Find additional eligible patients	Enable treatment of identified patients	Operationalize ocular gene therapy treatment centers	Secure coverage through traditional and novel models
Drive *RPE65* genetic testing	Educate on clinical value	Leverage robust patient support programs	Secure access through unique contracting arrangements

3Q in review: 24 vials shipped; patients now treated in 9 of 10 treatment centers, ~85% of commercial lives covered by acceptable medical policy

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Spark **P**ioneering **A**ccess **T**o **H**ealthcare (PATH): novel payment and distribution options to support patient access to LUXTURNA

Spark PATH is an innovative contracting and distribution model aiming to advance patient access while balancing the needs of all stakeholders

Innovative Contracting Model (ICM)	Direct sale to payer or specialty pharmacy as an alternative to traditional "buy and bill" model • Reduces financial burden and risk to the institution as well as mark-up to the payer • Coverage to label; expedited benefits processing; patient out-of-pocket cap
ICM + outcomes-based rebate arrangement	Outcomes-based rebate arrangement with both: • An initial efficacy (30-90 days) measure • A longer-term durability (30 months) measure
Discussions ongoing with CMS and HHS	Potential to enable Spark to offer outcomes-based installment payments focused on initial efficacy and long-term durability

First two patients treated under outcomes-based rebate model in 3Q

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Demonstrated leadership in applying gene therapy technology to the potential treatment of hemophilia

Objectives for developing optimized investigational gene therapies for hemophilia

Safety

- **Utilize** the **lowest** effective **dose** to reduce safety risks
- **Restore hemostasis** by leveraging **normal physiologic mechanisms**
- **No new risks** including prolonged transaminase elevations or thrombophilia
- Rapid clearance of **AAV**
- **No inhibitors**

Efficacy

- **All patients achieve** and **maintain clinically meaningful improvements**
  - Dramatic **reduction** in **bleeds**
- **Reduced treatment burden** and **improved QoL** with a **single dose**
  - Dramatic **reduction** in **infusions**
- **Durability** of **effect**
  - **Sustained outcomes supported by stable factor** activity without the marked PK troughs characterizing chronic therapies

Create value by solving significant unmet medical need and delivering cost offsets to the healthcare system

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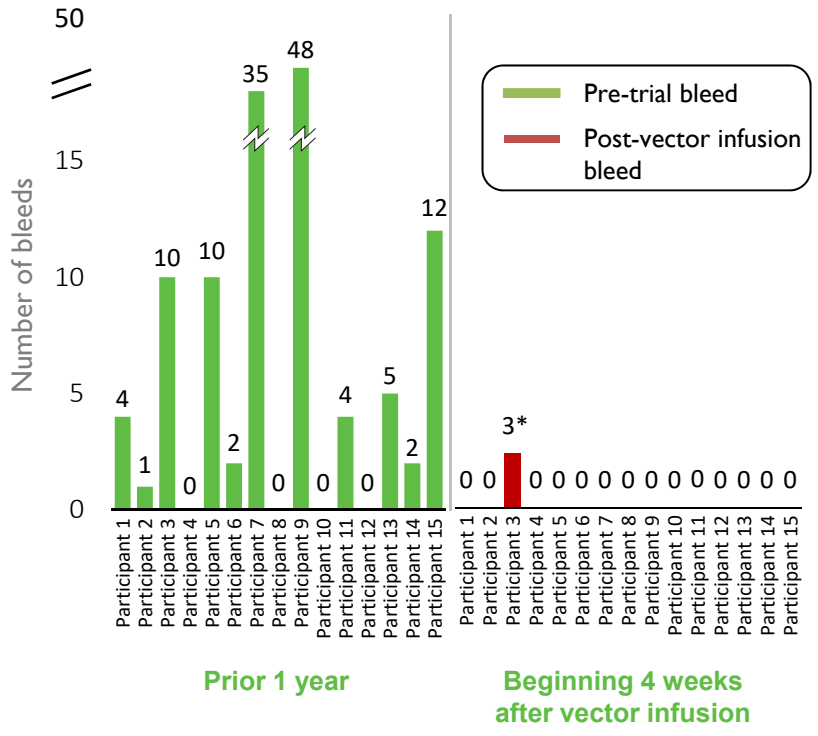
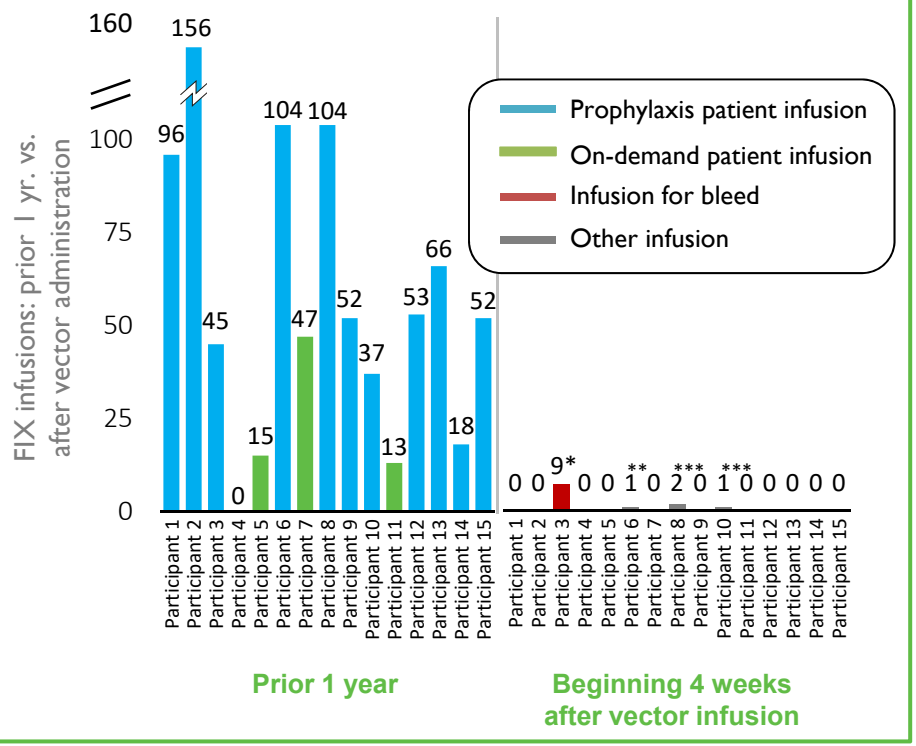
Preliminary fidanacogene elaparvovec Phase 1/2 data in hemophilia B: Predictable clinical outcomes for all 15 participants as demonstrated by near elimination of bleeds and infusions

98% reduction in mean bleeds beginning 4 weeks after vector infusion (97% beginning at time of vector infusion)



99% reduction in mean FIX infusions beginning 4 weeks after vector infusion (99% beginning at time of vector infusion)



No SAEs reported as of May 7, 2018, including no FIX inhibitors, no thrombotic events, and no sustained or unresolved elevations in LFTs

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Note: fidanacogene elaparvovec data as of May 7, 2018. The *SPK-9001* Phase 3 program is being conducted by Pfizer. For any questions regarding this program, please contact Pfizer

*Participant 3 self-infused factor concentrates for ankle bleed on Day 2 after vector infusion and self-administered precautionary infusions another nine times between Dec. 1, 2016 and Jan 2, 2017 for persistent knee pain. Participant has not used factor concentrates since Jan. 2, 2017.

** Participant 6 received infusion at End of Study visit.

*** Participant 8 received infusions for removal of mediport; Participant 10 received infusion for surgical procedure.

Investigational *SPK-8011* preliminary Phase 1/2 safety data as of July 13, 2018

- **No deaths**
- **1 SAE** – subject with elevated transaminases admitted to hospital for IV steroid administration following subtherapeutic response to oral steroids
- **3** subjects with **treatment-related AEs**:
  - Vomiting (mild), pyrexia (moderate), back pain (mild), myalgia (moderate) on day of infusion in one participant; events resolved in 1-3 days
  - **Liver-enzyme elevation AEs in two participants**; events **resolved in 7** and **17 days**
- **1** subject with **procedure-related AEs** – investigator **attributed to steroid therapy**
  - Adrenal insufficiency (mild) 148 days after infusion – resolved
  - Worsening stomach reflux (mild) 169 days after infusion – resolving
- **No detectable vector shedding in body fluids at 3 weeks**; clearance from **PBMC by week 12**
- **No inhibitor development**

Largely similar profile to that seen with *SPK-9001*

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Investigational *SPK-8011* preliminary Phase 1/2 clinical outcomes as of July 13, 2018

Reduction in bleeds:

- **97% reduction in bleeds** across all 12 participants dosed **at three dose levels**
- **No bleeds in the 5 (out of 7) 2e12 vg/kg subjects without significant** FVIII activity drop due to **immune response**

Reduction in infusions:

- **97% reduction** in **infusions** across all 12 participants dosed **at three dose levels**
- **All 2e12 participants** have **stopped using FVIII concentrates**, **except** for the **two who experienced significant** FVIII activity drops due to **immune response**

Durability:

- The **first two participants**, with **follow-up over one year**, have shown **consistent outcomes** and **stable FVIII levels up to 66 weeks** as of July 13, 2018, with **follow-up ongoing**

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Note: Data as of July 13, 2018 cutoff for last public update. Data on bleeds and infusions as of >4 weeks post-vector infusion.

Next steps for hemophilia A program

- **Expanding Phase 1/2 study of** investigational ***SPK-8011*** **with two modifications:**
  - Dose participants with **material made from suspension process**
  - Standardize **prophylactic steroid regimen**
- **Begin enrollment of Phase 3** run-in study **by YE18**
  - **Multinational Phase 3** trial planned
  - **Input from continued dialogue with FDA** under Breakthrough Designation **incorporated into Phase 3** program **design**
- **Progress** development of investigational ***SPK-8016*** **for** hemophilia A **inhibitor market**
  - **Starting in non-inhibitor patients** to evaluate **safety**

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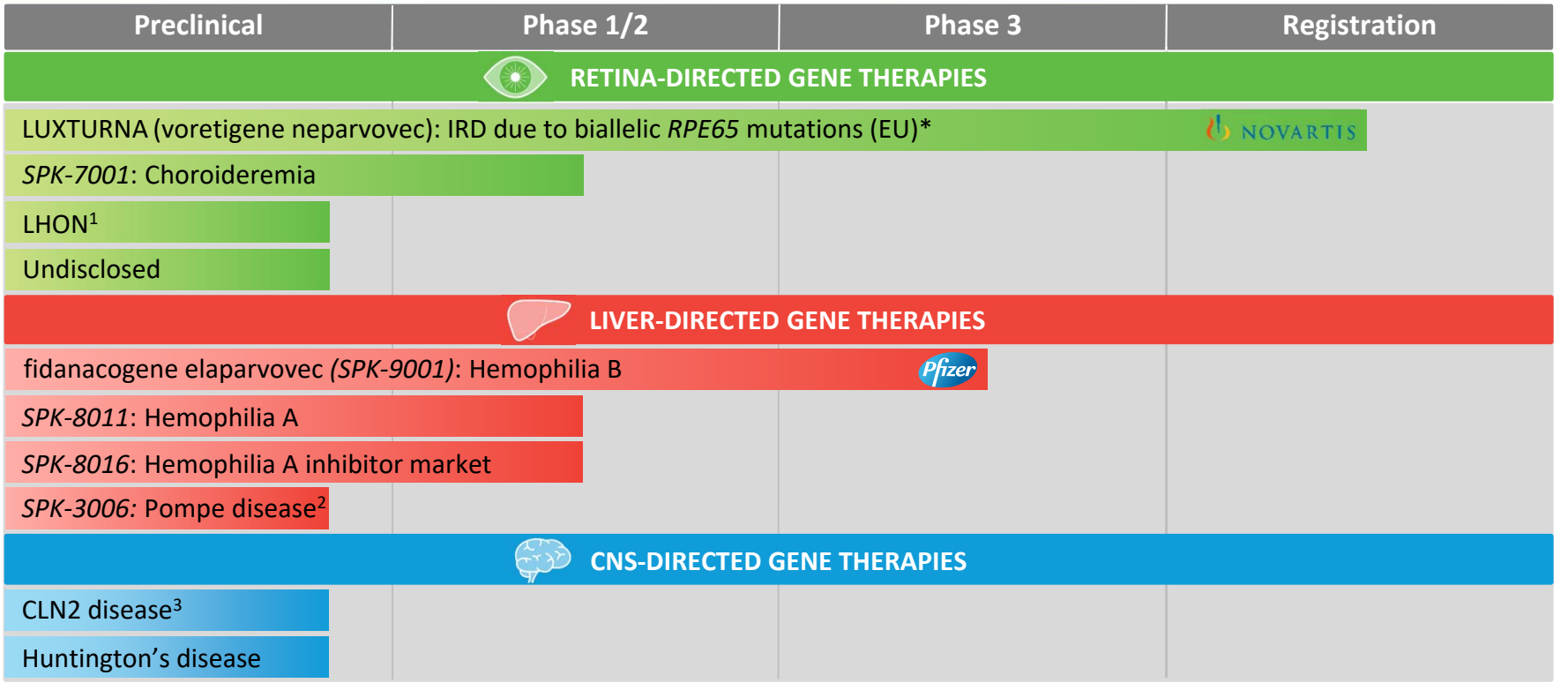
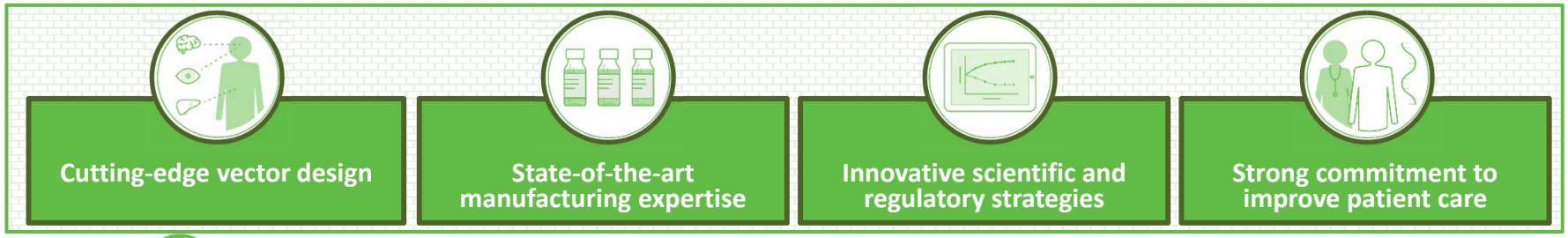
Fully integrated AAV gene therapy platform and pipeline

Spark development pipeline

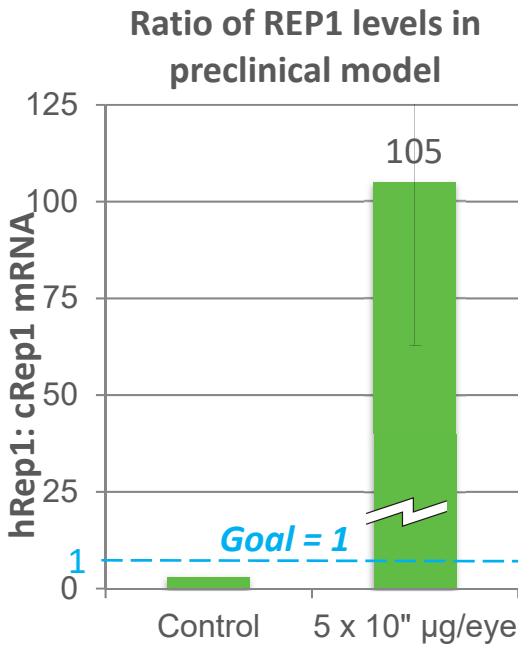




[1]Leber hereditary optic neuropathy; [2]Initial construct licensed from Genethon; [3]Form of Batten Disease.
*Approved in the US; MAA validated and under review in EU, with ex-US rights licensed to Novartis.

Interim data from ongoing *SPK-7001* Phase 1/2 trial in CHM: No product-related SAEs with 15 participants dosed; follow-up ongoing

- Choroideremia is slow-progressing, affecting ~**12,500** males in US / EU5
- To study safety, initiated 2-year Phase 1/2 trial in 10 participants with later-stage disease
  - *SPK-7001* administration resulted in **no product-related SAEs**
- At interim analysis[1], 4 of 10 later-stage participants showing **non-statistically significant indications of efficacy** on 1 or more endpoints
  - Non-significance of results may be due to duration of follow-up and later-stage of disease in this cohort
- **Completed enrollment** in additional cohort of 5 participants at an **earlier-stage of disease**
- **Next steps**: Plan to conduct and share additional analyses of both earlier- and later-stage disease cohorts YE18



Source: Spark unpublished preclinical data.

[1] At time of interim analysis (May 2017), had 1 year of follow-up on 5 participants, 18 months of follow-up on 4 and the targeted 2-year data for 1

A novel, liver-directed investigational approach to the treatment of Pompe disease

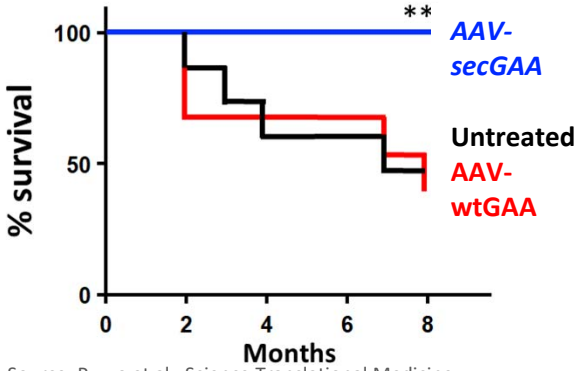
Current SoC: GAA enzyme replacement

- Chronic replacement of recombinant form of missing enzyme (*wtGAA*) results in limited efficacy in many affected patients, specifically in certain refractory tissues
- Peaks and troughs in plasma concentration of *GAA*
- High patient burden and cost of treatment
- Potential for immunogenicity in some patients

AAV-secGAA:

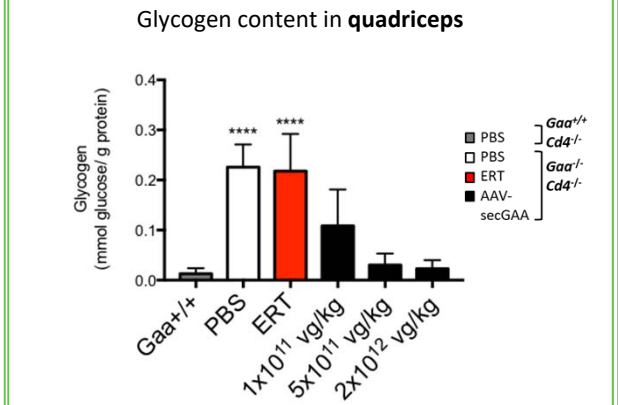
- Novel secretable, modified *GAA* transgene (*secGAA*)[1] engineered for efficient secretion into plasma
- Early evidence of glycogen clearance throughout the body – including in refractory tissues – seen with sustained plasma levels driven by one-time administration of AAV-*secGAA*
- Early evidence of reduced immunogenicity of *secGAA* (vs. native) *GAA* in Pompe mice

AAV-secGAA's secretable _GAA_ transgene expression resulted in greater rescue of Pompe mouse model vs. AAV-wtGAA



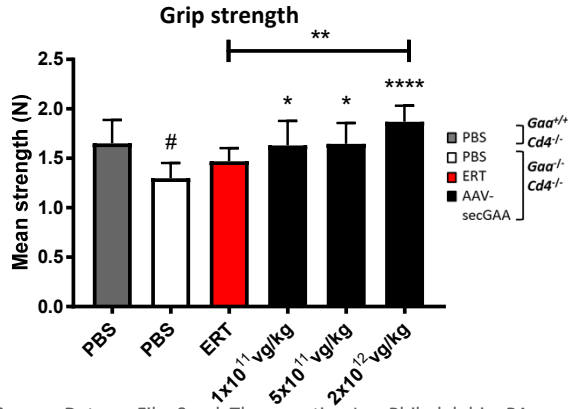
Source: Puzzo et al., Science Translational Medicine 2017 and unpublished results

AAV-secGAA gene transfer in Pompe mouse model resulted in significantly reduced glycogen storage vs. SoC in refractory tissues



Source: Data on File. Spark Therapeutics, Inc. Philadelphia, PA.

AAV-secGAA demonstrated highly statistically significant benefit vs. SoC in Pompe mouse model functional outcomes



Source: Data on File. Spark Therapeutics, Inc. Philadelphia, PA.

Estimated prevalence / incidence of Pompe disease: **~6,000-8,000 / ~200-400 in US + EU5**

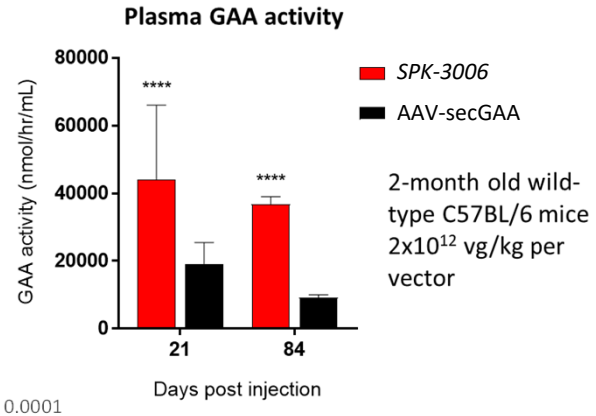
**** p<0.0001; ** p<0.01; * p<0.05 (vs. $Gaa^{-/-}$ PBS in left and right panels; vs. $Gaa^{+/+}$ in center panel) except when noted; # p<0.05 vs. $Gaa^{+/+}$; One-way ANOVA, with Dunnett's multiple comparisons test

(1) Intellectual property for *secGAA* licensed from Genethon

Investigational *SPK-3006*: Data from IND-enabling studies support moving optimized *AAV-secGAA* candidate into the clinic in 2019

- *SPK-3006* is an optimized form of *AAV-secGAA,* expressing the same secretable, modified GAA transgene product incorporated in a bioengineered capsid with a highly-efficient promoter
- Dose-finding study conducted in NHP at three ascending doses; clear dose-response seen
  - Through six months of follow-up, no documented vector-related toxicities observed to date at any dose in NHP from dose-finding study; long-term follow up ongoing
- Pre-IND meeting with FDA conducted, GLP toxicology and biodistribution study ongoing

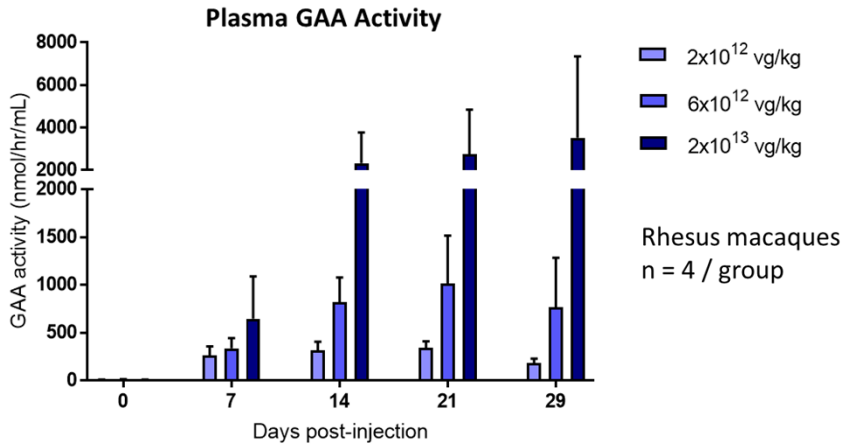
Plasma GAA activity post-*SPK-3006* infusion increased vs. *AAV-secGAA*



**** p < 0.0001

Data on File. Spark Therapeutics, Inc. Philadelphia, PA.

Single infusion of *SPK-3006* demonstrated dose-dependent increase in GAA activity at three ascending doses



Data on File. Spark Therapeutics, Inc. Philadelphia, PA.

Next steps: **Complete GLP toxicology** study and submit **IND and CTA filings;** if accepted, targeting initiation of **Phase 1/2 trial in 2019**

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Spark's unparalleled AAV manufacturing capabilities have been inspected and cleared by regulatory agencies and partners

Established adherent manufacturing process and capabilities

- Purpose-built, multi-suite, **in-house cGMP facility licensed by FDA** and **successful inspection by EMA**
- **In-house manufacturing** of worldwide commercial LUXTURNA supply **for Novartis and** initial Phase 3 fidanacogene elaparvovec material for **Pfizer**
- Adherent-cell culture (**HEK293** mammalian cell line), transient transfection process
- **41 assays** developed in-house, being run in production and release of LUXTURNA
- Implemented a **scalable all-column downstream** purification process

Sufficient scale for IRDs (including LUXTURNA™) and Hemophilia B

Successfully implemented commercial-scale suspension manufacturing capabilities

- Spark has achieved **successful scale up to target capacity of 200L** of a serum-free **suspension cell culture system**
  - Utilizes a **Spark-developed process** with our current **HEK293** cell line
- **Dedicated manufacturing capacity secured** at Brammer Bio **to manufacture *SPK-8011* trial material** using this successfully scaled process
- **Comparability** of suspension material **to adherent material being confirmed**

Sufficient scale to meet supply needs for hemophilia A Phase 3 clinical development and expected commercial requirements

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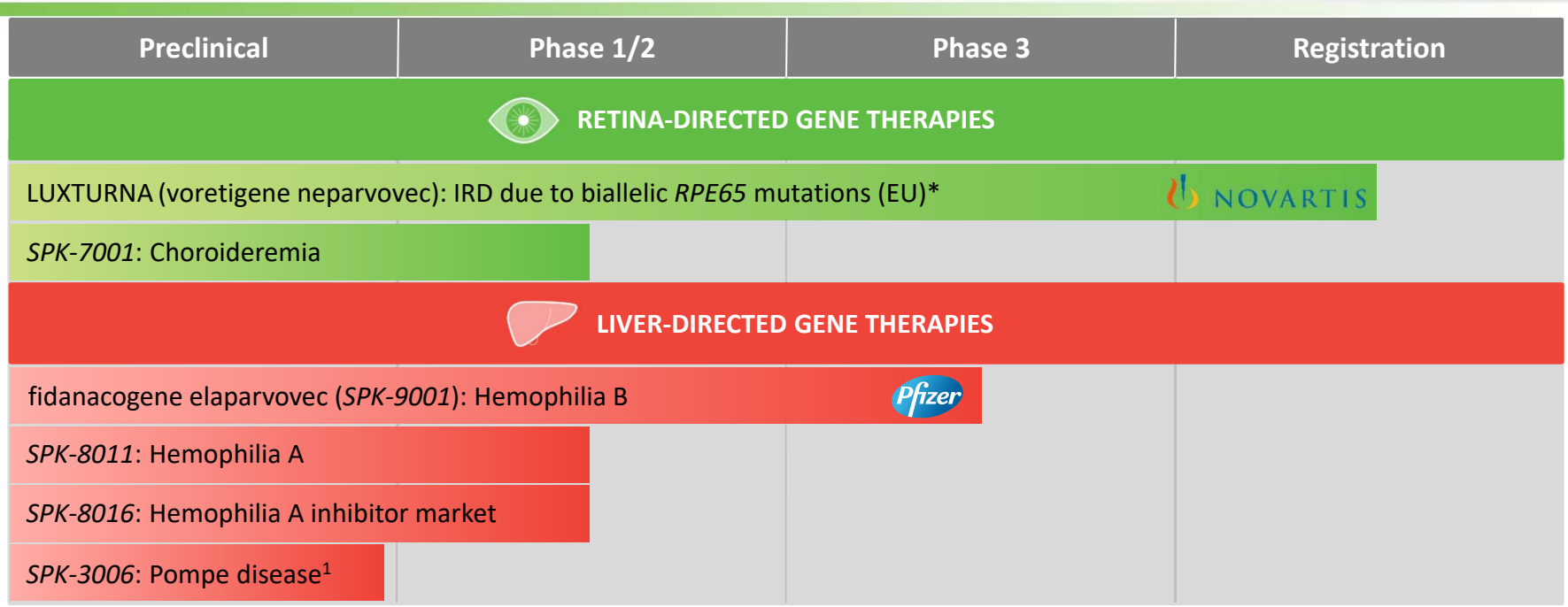
A catalyst rich 2018



Retina-directed gene therapy catalysts

- ✓ **January 2018:** Investigational LUXTURNA ex-US rights licensed to Novartis
- ✓ **End of 1Q18:** LUXTURNA (voretigene neparvovec-rzyl) available in the United States
- ✓ **1Q18:** First patients treated with LUXTURNA
- ✓ **2Q18:** Sale of priority review voucher
- ✓ **3Q18:** Positive CHMP opinion for LUXTURNA
- ● **Expected 4Q18:** EC regulatory action
- ● **Expected YE18:** Update on maturing *SPK-7001* dataset

Liver-directed gene therapy catalysts

- ✓ **1Q18:** Completed enrollment of additional *SPK-9001* Phase 1/2 participants
- ✓ **May 2018:** Demonstrated comparability of all-column downstream *SPK-9001* material in Phase 1/2 participants
- ✓ **July 2018:** Transitioned *SPK-9001* to Pfizer; Phase 3 initiated
- ✓ **August 2018:** *SPK-8011* Phase 1/2 clinical data update
- ✓ **October 2018:** *SPK-3006* preclinical data and program update
- ● **Expected by YE18:** *SPK-8011* Phase 3 run-in study initiation

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[1]Initial construct licensed from Genethon.