Spark Therapeutics, Inc.

Corporate Overview
October 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* 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) the improvements in functional vision demonstrated by LUXTURNA in our clinical trials may not be sustained over extended periods of time; (ii) we may not achieve our expected objectives for commercialization for LUXTURNA; (iii) voretigene neparvovec may not be approved in any markets outside of the U.S.; (iv) if approved, Novartis may not be successful in commercializing or selling voretigene neparvovec in one or more markets; (v) we may not receive any additional milestone or royalty payments from Novartis, Pfizer or our other collaborators; (vi) our early preliminary clinical results for our product candidate, *SPK-8011*, for hemophilia A may not be sustained; (vii) our implementation of a prophylactic approach to steroid administration for subjects participating in our *SPK-8011* clinical trials may not prevent an immune response; (viii) we may not be successful in initiating a Phase 3 clinical trial for *SPK-8011* and the timing and design of such trial may vary from our expectations; (ix) we are unable to maintain or continue to enter into agreements with payers for the provision of LUXTURNA; (x) our proposal to the Centers for Medicare & Medicaid Services (CMS) is not accepted; (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; and (xii) 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**
  - EMA **CHMP positive opinion; EC action** expected **4Q18**
- Investigational **fidanacogene elaparvovec** (formerly *SPK-9001)* for **hemophilia B: Transition** to Pfizer **completed**; **Phase 3 program initiated**
- Investigational ***SPK-8011*** for **hemophilia A:** Plan to **take 2x10^{12} vg/kg dose into Phase 3** clinical trials, beginning with a run-in study, **by YE18; dose-response** demonstrated in Phase 1/2 trial
- Investigational ***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:
  - **Commercial-scale adherent and suspension** process **capabilities** established; **First** and **only FDA-approved AAV commercial manufacturing facility**
  - **Follow-up ongoing** for investigational ***SPK-7001*** Phase 1/2 trial **in choroideremia**
- **$656.8 million** in cash and equivalents at 6/30/18

Spark THERAPEUTICS

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 within 60 days thereafter

Spark THERAPEUTICS

*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**	**Seamless supply chain**

1H in review: U.S. launch ongoing with 18 vials shipped; patients now treated in 6 of 9 treatment centers, 80% of commercial lives covered by acceptable medical policy

Spark THERAPEUTICS

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**
Continue to advance ongoing discussions with CMS and HHS	Potential to enable Spark to offer **outcomes-based installment payments** focused on initial efficacy and long-term durability

Spark THERAPEUTICS

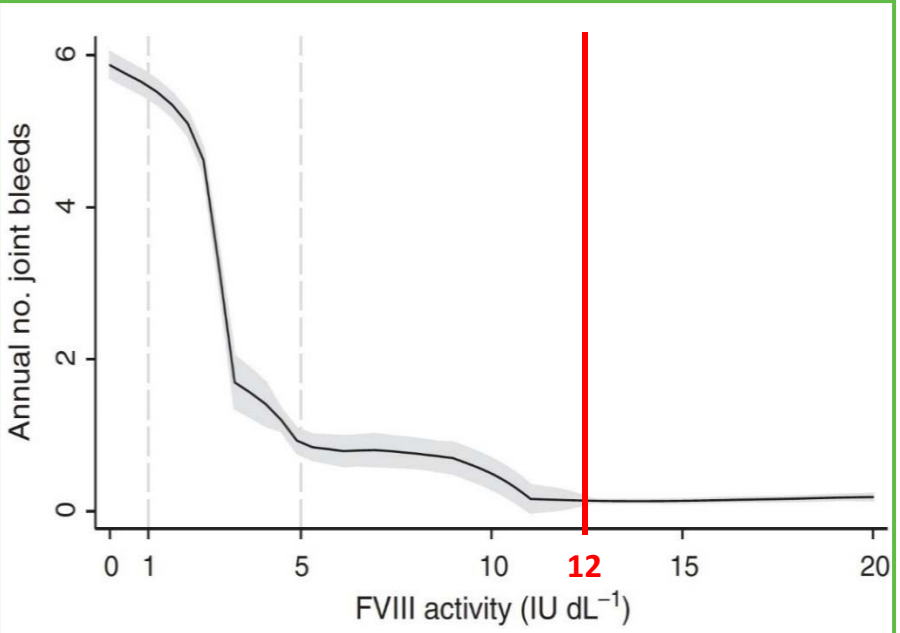
Spark THERAPEUTICS

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

Spark objectives for developing an optimized gene therapy for hemophilia

- **Safety**
  - **Low,** effective **dose** to reduce risk of SAEs
  - **Restore hemostasis by leveraging innate biology** rather than bypassing normal physiological pathways
  - **No new risks or inhibitors**
- **Predictable clinical outcomes**
  - Participants **achieving clinically meaningful outcomes based on sufficient factor activity** without exceeding factor levels that could introduce new safety risks
- **Durable** factor expression
  - Without the troughs that characterize regular infusions of protein therapeutics
  - Reduce treatment burden and improve QoL

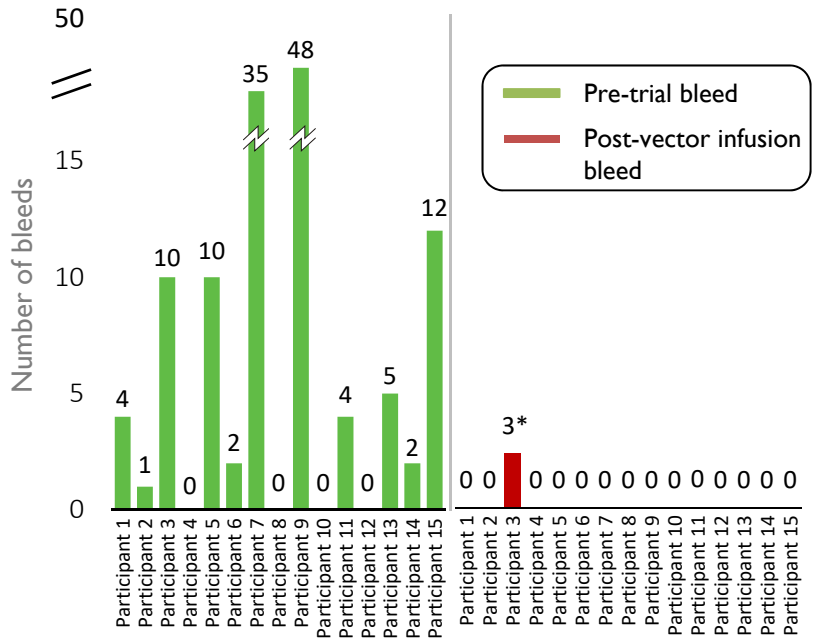
Factor activity levels >12% at all times reduces risk of bleeds and need for chronic infusions



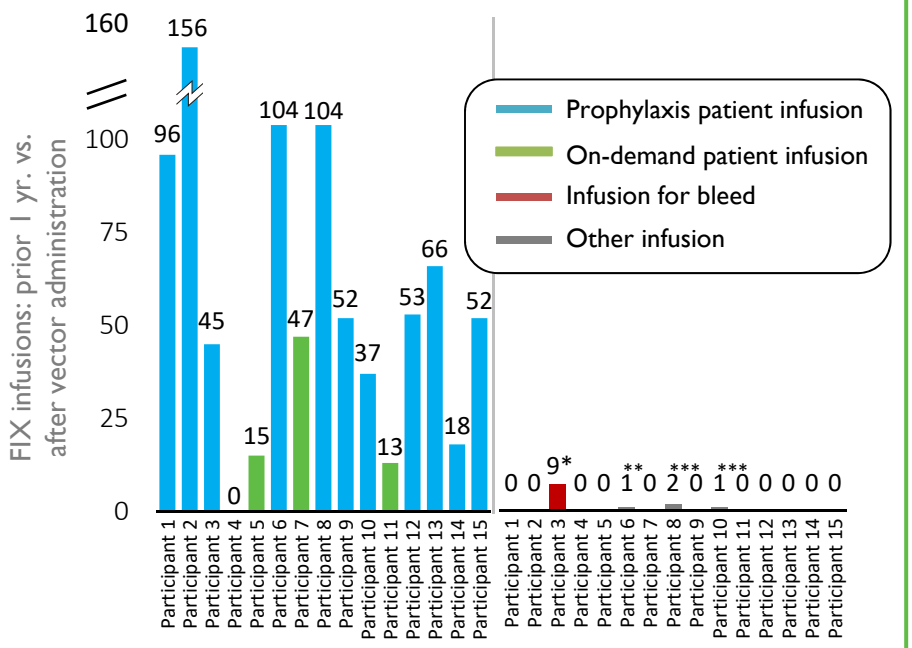
Note: Black lines are medians; shaded areas interquartile ranges.
Source: Adapted from den Uijl IE *et. al.* Haemophilia 2011; 17(6):849-53.

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 ABR beginning 4 weeks after vector infusion (97% beginning at time of vector infusion)



99% reduction in mean AIR 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

Spark THERAPEUTICS

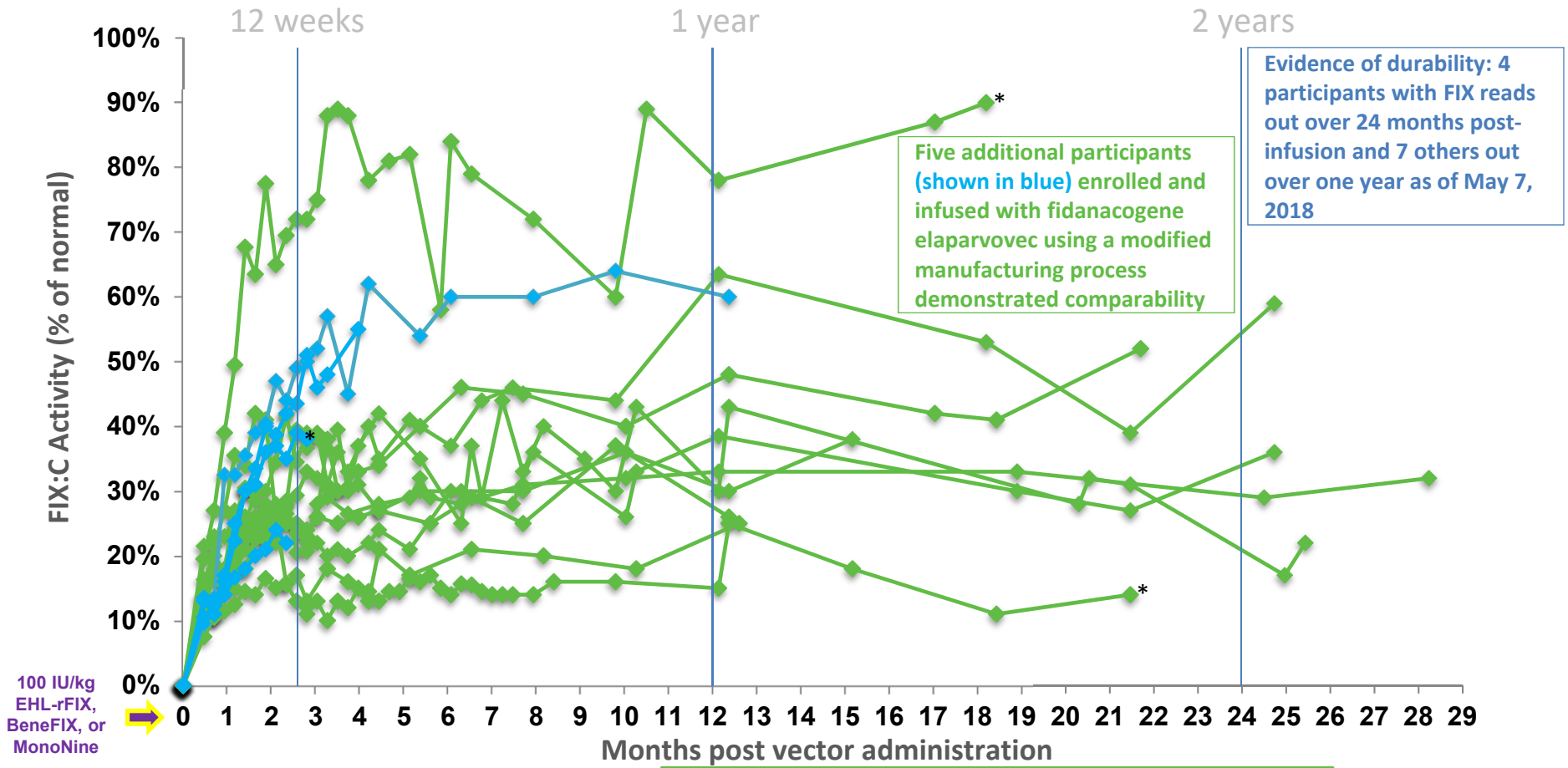
Note: fidanacogene elaparvovec data as of May 7, 2018.

*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.

Preliminary fidanacogene elaparvovec Phase 1/2 data in hemophilia B: Consistent and durable FIX activity within target range through 2 years



* Three fidanacogene elaparvovec trial participants experienced asymptomatic, transient elevation in liver enzymes, or decline in FIX activity, potentially indicative of an immune response to the Spark100 capsid. Two of these cases were recorded as adverse events related to the investigational product, with one participant experiencing LFT elevation above normal limits. All three received a tapering course of corticosteroids, after which LFT elevations resolved.

Note: Plotted values represent weekly averages for each of initial 14 participants.
Source: Spark data as of May 7, 2018;
FIX:C Activity = circulating factor IX activity level
EHL-rFIX – Extended half-life recombinant factor IX

Spark THERAPEUTICS

Preliminary *SPK-8011* Phase 1/2 data in hemophilia A: Spark is two for two in achieving proof-of-concept in investigative hemophilia gene therapy

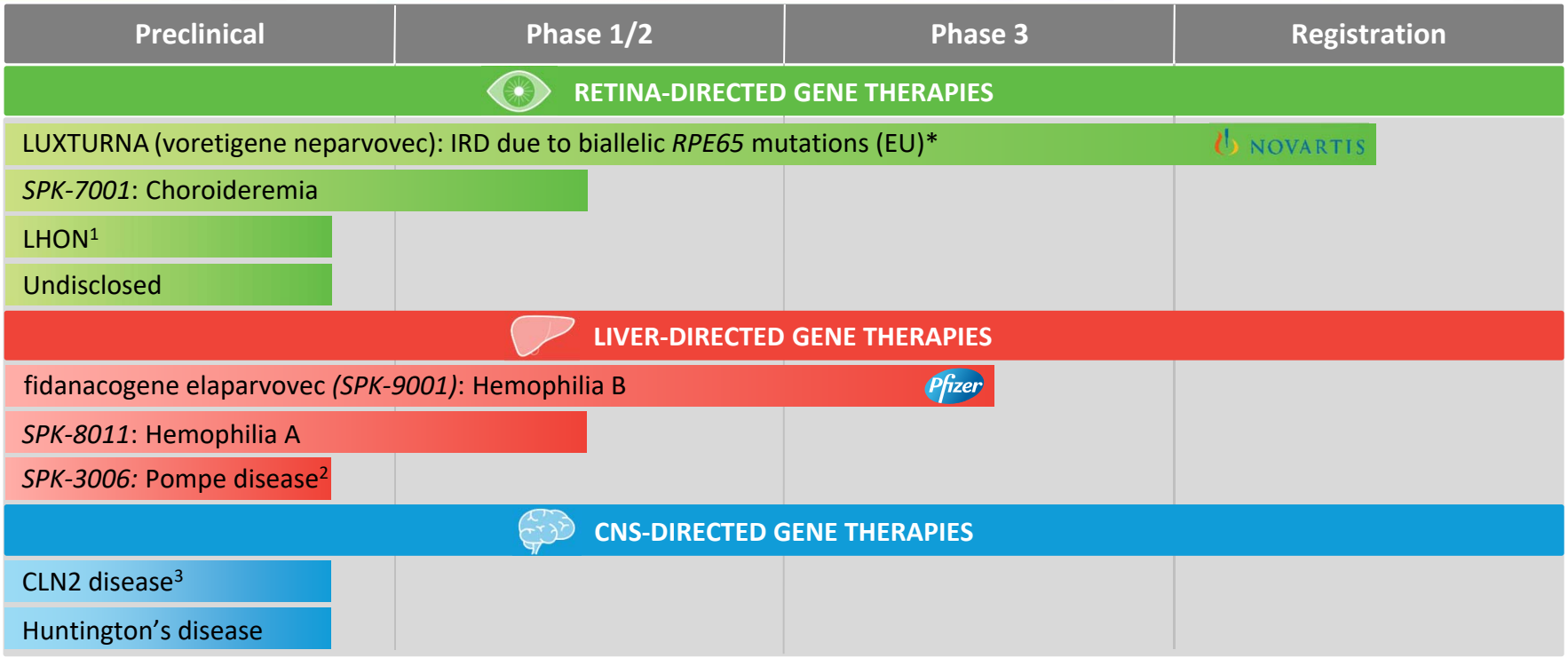
	***SPK-8011* for hemophilia A**
Safety	• **No FVIII inhibitors, no thrombotic events, and no sustained or unresolved elevations in LFTs** as of July 13, 2018 • **1 SAE reported** due to participant admission to hospital for IV steroid administration to treat **asymptomatic immune response** not resolving with oral steroids, after which the **event resolved**
Evidence of predictability of clinical outcomes	• **Predictability of clinical outcomes: 97%[1] reduction in mean ABR and AIR** in 12 participants as of July 13, 2018 • **Consistent FVIII activity** achieved **in five of the participants in 2x10^{12} vg/kg cohort,** with follow-up ranging from 12 to 30 weeks – **FVIII** expression ranging **from 16% to 49%; mean of 30% FVIII** post 12-weeks (**in line with** results seen with ***SPK-9001***) resulting in **ABR/AIR of 0**[1] • Remaining **two 2x10^{12} vg/kg participants** had an **immune response** that **caused** their **FVIII levels to decline to less than 5%** – **Both** have **moved from prophylactic to on-demand** treatment, seeing **meaningful ABR/AIR reductions** • **Implementing prophylactic steroid administration** moving forward**; expect** this protocol to **suppress immune responses** and lead to **long-term expression of FVIII above 12% in all participants at 2x10^{12} vg/kg** dose
Evidence of durability	• The first two participants, with follow-up over one year, have shown **stable FVIII levels since reaching plateau up to 66 weeks** as of July 13, 2018, with follow-up ongoing

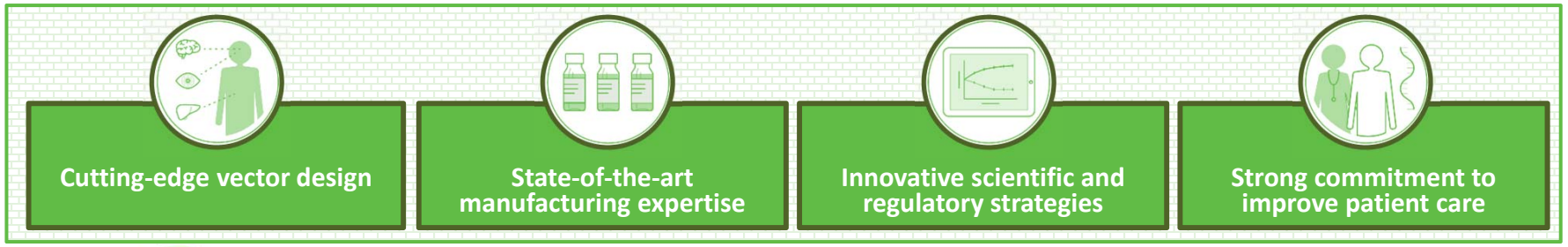
Data as of July 13th, 2018.
Note: Seven of twelve participants in *SPK-8011* Phase 1/2 trial were put on tapering course of corticosteroids in response to ALT elevation above baseline, declining FVIII levels and/or positive ELISPOTs. For these seven participants, steroids led to normalization of ALT and ELISPOTs. For all but two 2x10^{12} vg/kg cohort participants, oral steroids also led to stabilization of FVIII levels above 12 percent.
Source: *SPK-8011* preliminary initial Phase 1/2 data per trial database. Factor activity refers to FVIII:C values from local labs.
(1) Calculated starting four weeks post-vector infusion.

Spark THERAPEUTICS

Fully-integrated AAV gene therapy platform and pipeline

Spark development pipeline

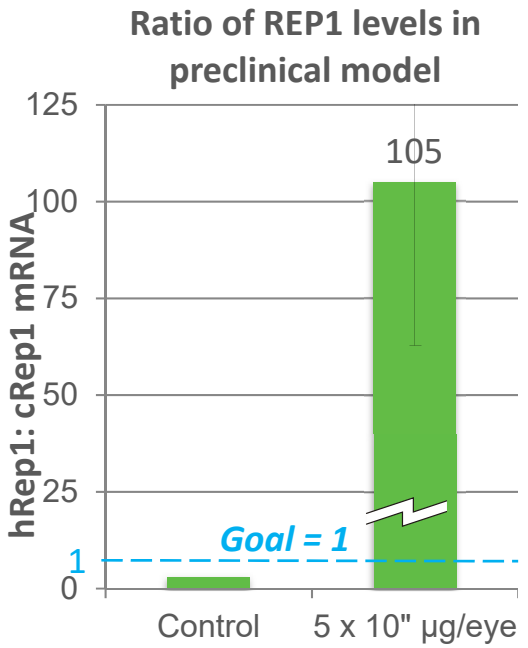




[1]Leber hereditary optic neuropathy; [2]Initial construct licensed from Genethon; [3]Form of Batten Disease.
*Approved in the US; MAA validated and under review in EU, with ex-US rights licensed to Novartis.

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 in 4Q18



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

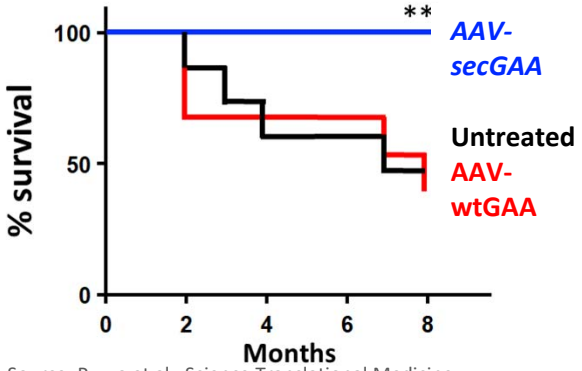
Current SoC: GAA enzyme replacement

- 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:

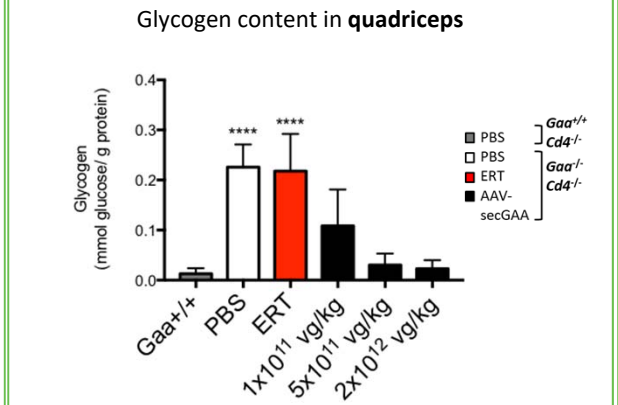
- Novel secretable, modified *GAA* transgene (*secGAA*)[1] engineered for efficient secretion into plasma
- Early evidence of glycogen clearance throughout the body – including in refractory tissues – seen with sustained plasma levels driven by one-time administration of AAV-*secGAA*
- Early evidence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



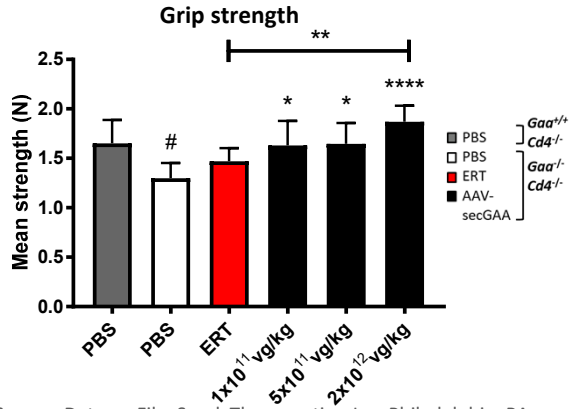
Source: Puzzo et al., Science Translational Medicine 2017 and unpublished results

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**

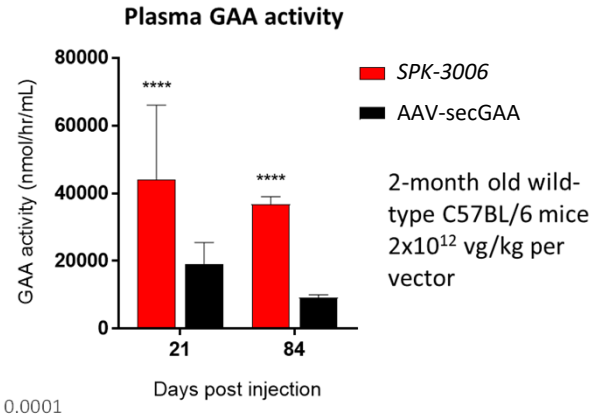
**** p<0.0001; ** p<0.01; * p<0.05 (vs. $Gaa^{-/-}$ PBS in left and right panels; vs. $Gaa^{+/+}$ in center panel) except when noted; # p<0.05 vs. $Gaa^{+/+}$; One-way ANOVA, with Dunnett's multiple comparisons test

(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

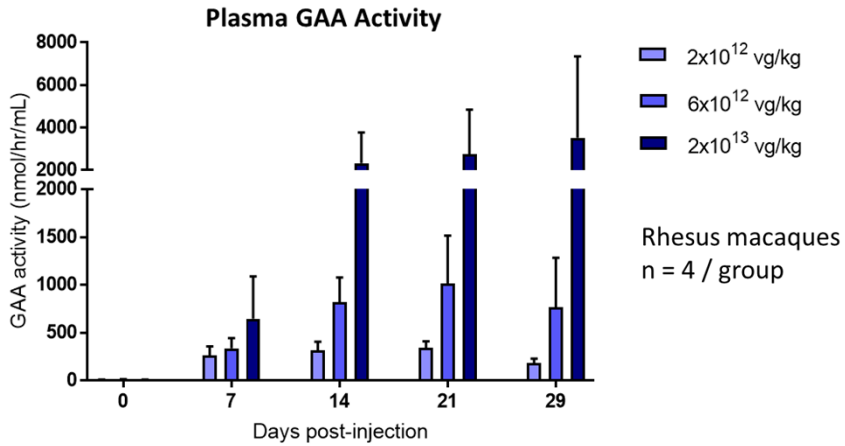
Plasma GAA activity post-*SPK-3006* infusion increased vs. *AAV-secGAA*



**** 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**

Spark THERAPEUTICS

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 approved 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
- **24 assays** developed for, and being used in, production of LUXTURNA
- Implemented a **scalable all-column downstream** purification process

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

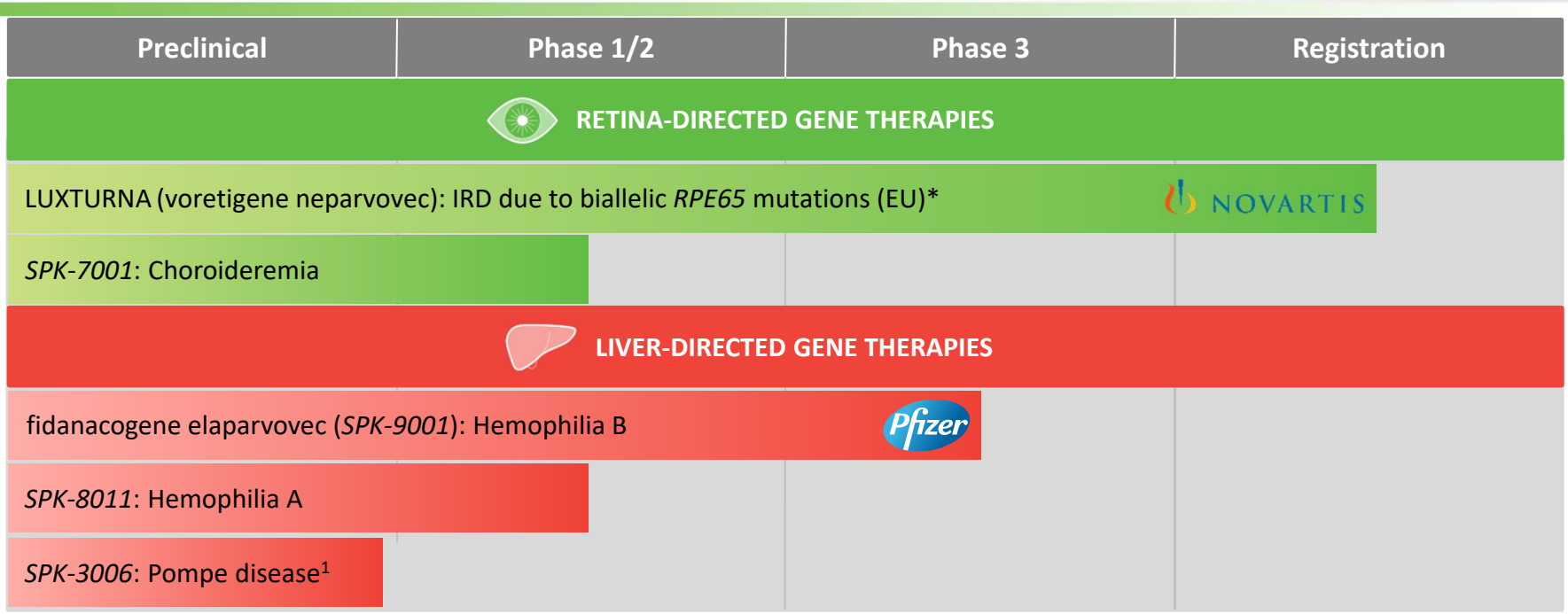
Successfully implemented commercial-scale suspension manufacturing capabilities

- 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 to be confirmed** as part of continued dosing **in *SPK-8011* Phase 1/2 trial**

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

Spark THERAPEUTICS

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 4Q18:** 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

Spark THERAPEUTICS

*Approved in the US; MAA validated and under review in EU, with ex-US rights licensed to Novartis.
[1]Initial construct licensed from Genethon.