Spark Therapeutics, Inc.

Corporate Overview
June 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) our MAA for LUXTURNA may not be approved by EMA; (ii) the data from our Phase 3 clinical trial of LUXTURNA may not support labeling for all biallelic *RPE65* mutations other than Leber congenital amaurosis (LCA) in ex-US geographies; (iii) the improvements in functional vision demonstrated by LUXTURNA in our clinical trials may not be sustained over extended periods of time; (iv) voretigene neparvovec may not be approved in any markets outside of the U.S.; (v) upon approval, 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 or sufficient to support further development; (viii) we may be unsuccessful in achieving higher factor VIII activity levels through dose escalation in our Phase 1/2 clinical trial of *SPK-8011*; (ix) our early preliminary data in our Phase 1/2 clinical trial of *SPK-8011* have yet to be audited and therefore are subject to confirmation in connection with a clinical trial audit; (x) we do not enter into successful agreements with commercial insurers to make LUXTURNA available for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy; (xi) our payer and patient offerings will not ensure eligible patients have the coverage and financial support they need to gain access to LUXTURNA and the required specialized medical care; (xii) payers terminate any agreements they enter into with us; (xiii) our proposal to the Centers for Medicare & Medicaid Services (CMS) is not accepted; (xiv) our lead *SPK-FIX* product candidate, *SPK-9001*, may not produce sufficient data in our Phase 1/2 clinical trial to warrant further development; (xv) 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; (xvi) we may not complete IND-enabling studies for *SPK-GAA* when we anticipate, or at all; and (xvii) 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 press release is as of the date of the release, and Spark undertakes no duty to update this information unless required by law.

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

- **LUXTURNA** is the **first gene therapy** for a genetic disease in the US
  - **US launch underway**
  - **EU** registration **in process**, with **ex-US rights** licensed to **Novartis Pharmaceuticals**
- Investigational ***SPK-9001*** for **hemophilia B** Phase 1/2 compelling safety and clinical outcomes data presented at WFH: **98% reduction in ABR[1] and 99% reduction in AIR[1] seen**
  - Expect to complete **transition to Pfizer mid-year** to **enable Phase 3 initiation**
- Investigational ***SPK-8011*** for **hemophilia A** granted breakthrough designation by FDA
  - **7 participants infused as of 12/6/17** at three doses: $5x10^{11}$ vg/kg; $1x10^{12}$ vg/kg; and $2x10^{12}$ vg/kg
  - **Dose-finding ongoing** with data in 3Q18
- A **fully-integrated** adeno-associated virus **(AAV) gene therapy platform** and **pipeline** of clinical and preclinical candidates across multiple target tissues:
  - **First** and **only FDA-approved AAV commercial manufacturing facility**
  - **Follow-up ongoing** for investigational *SPK-7001* Phase 1/2 trial **in choroideremia**
  - **Third** liver-directed disease **target: Investigational Pompe disease** program utilizing a novel secretable transgene
- **$587.5 million** in cash and equivalents at 3/31/18
  - **Additional $110 million** received for **sale of priority review voucher**

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(1) Calculated starting four weeks post-vector infusion.

LUXTURNA: US launch underway (voretigene neparvovec-rzyl)

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 *RPE65* patients is left to the **clinical judgment of the treating physician**
- Labeling supports claim of **durability out to three years**
- Clearly described **safety profile**

LUXTURNA™
voretigene neparvovec-rzyl
for subretinal injection

LUXTURNA proceeding through EU registration process with action expected in 3Q18; recent successful EMA inspection of Spark manufacturing facility

Ex-US rights licensed to Novartis Pharmaceuticals*

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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 conversion of known 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**

1Q in review: First three patients treated; agreements in place with nine treatment centers; 60% of commercial lives with satisfactory medical coverage

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Spark 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**
On-going discussions with Centers for Medicare & Medicaid Services (CMS)	Potential to enable Spark to offer **outcomes-based installment payments** focused on initial efficacy and long-term durability

LUXTURNA wholesale acquisition cost: $425,000 per eye

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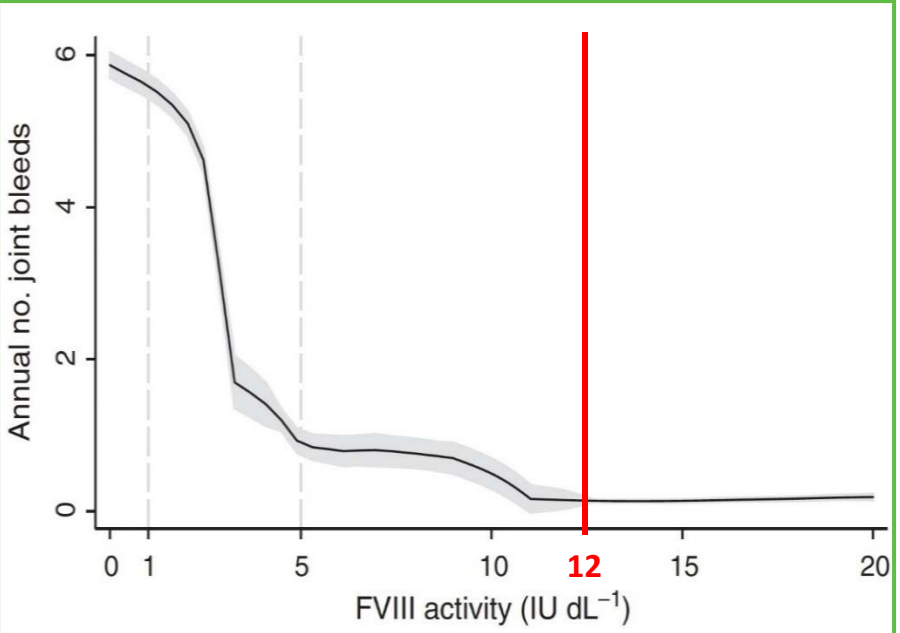
Demonstrated leadership in applying gene therapy technology to the potential treatment of hemophilia

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
- **Sustained** 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.

Spark is two for two in achieving proof-of-concept in hemophilia gene therapy

	SPK-9001 for hemophilia B (Spark, Pfizer)	*SPK-8011* for hemophilia A (Spark)
Safety	• **No SAEs reported**, including no FIX inhibitors and no thrombotic events as of May 7, 2018	• **No SAEs reported**, including no FVIII inhibitors and no thrombotic events as of December 6, 2017
Evidence of predictability of clinical outcomes	• **Predictability of clinical outcomes: 98%[1] reduction in mean ABR and 99%[1] reduction in mean AIR** in more than 18 cumulative years of follow-up, as of May 7, 2018 • **Consistent FIX activity** levels achieved – **14 participants** with data through at least 12 weeks of follow-up as of May 7, 2018 are within an **acceptable range**	• **First 4 participants free of bleeds** beginning 4-weeks post-vector infusion, with **98% reduction in mean AIR[1]** in ~2 cumulative years of follow-up as of December 6, 2017 • As of 12/6/17, **three additional participants** have been dosed (1 at $1x10^{12}$ and 2 at $2x10^{12}$) • **Therapeutic FVIII levels** seen in **first 4 participants**: average factor levels after 12 weeks for $5x10^{11}$ participants of 10% and 16% and for $1x10^{12}$ participants of 9% and 13% as of December 6, 2017
Evidence of sustainability	• **Sustained FIX expression** with 4 participants with FIX reads out over 24 months post-infusion and 7 others out over one year as of May 7, 2018	• First participant out over 9 months, and second, third and fourth participants out ~3-6 months post-infusion as of December 6, 2017

Data as of May 7, 2018 for *SPK-9001* and December 6th, 2017 for *SPK-8011*.
Note: Three *SPK-9001* 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 investigational product, with only one participant seeing LFT elevation above normal limits. All three received a tapering course of corticosteroids. As of May 7, 2018, none of these participants experienced a bleed, but one participant received an infusion to treat a rolled left ankle. Participants 3 and 4 in *SPK-8011* Phase 1/2 trial were put on tapering course of corticosteroids after drop in FVIII activity levels observed; prednisone stopped on November 28th and 26th, 2017, respectively.
Source: *SPK-8011* and *SPK-9001* preliminary initial Phase 1/2 data per trial database. Factor activity refers to FVIII:C or FIX:C values from local labs.
(1) Calculated starting four weeks post-vector infusion.

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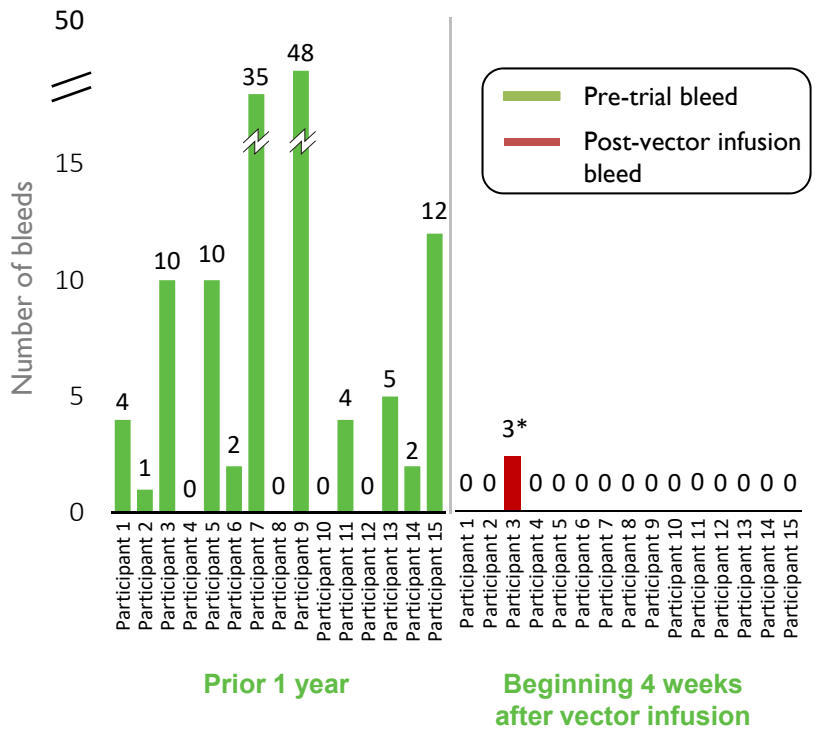
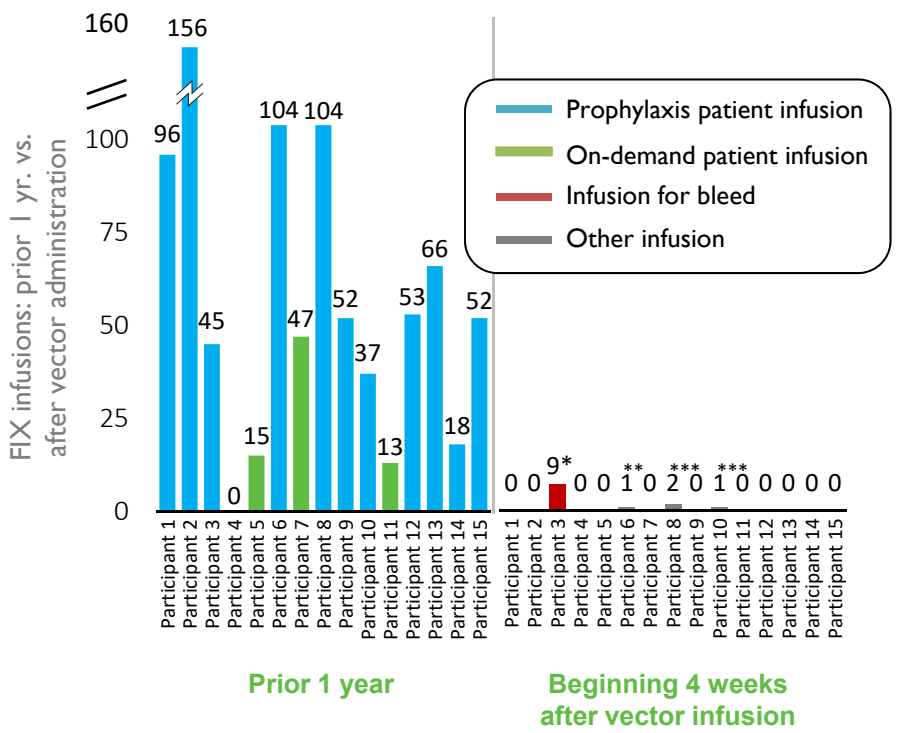
Preliminary *SPK-9001* Phase 1/2 data in hemophilia B: Predictable clinical outcomes for all 15 participants as demonstrated by near elimination of bleeds and infusions

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)



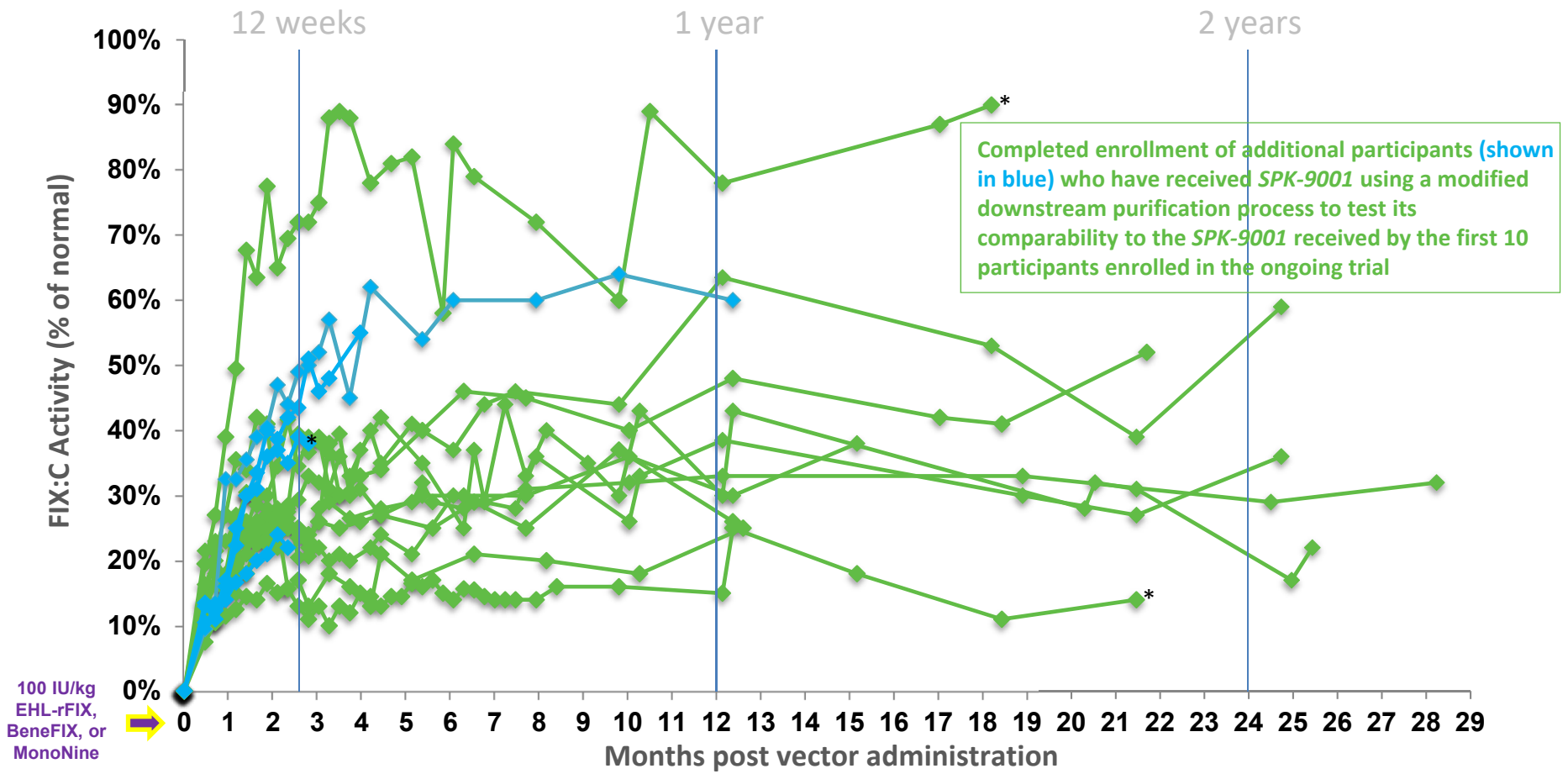
Note: *SPK-9001* data as of May 7, 2018.

*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 *SPK-9001* Phase 1/2 data in hemophilia B: Consistent and sustained FIX activity within target range in initial 14 participants

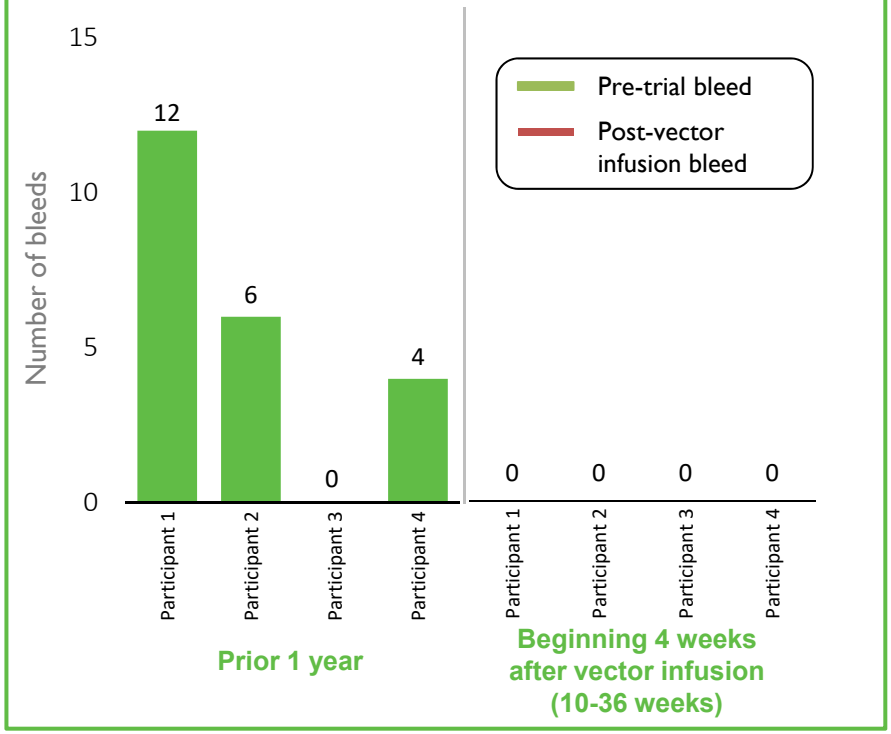


Note: Plotted values represent weekly averages for each participant.
Source: Spark data as of May 7, 2018;
FIX:C Activity = circulating factor IX activity level
EHL-rFIX – Extended half-life recombinant factor IX

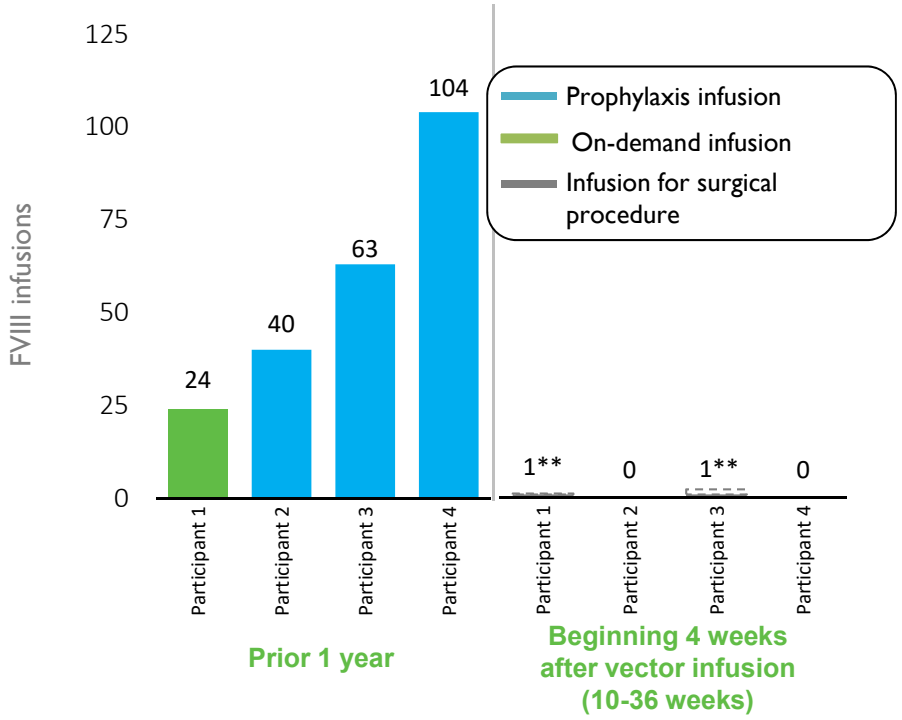
* Three *SPK-9001* trial participants experienced asymptomatic, transient elevation in liver enzymes, or decline in FIX activity, potentially indicative of an immune response to the Spark100 capsid. Two of these cases were recorded as adverse events related to the investigational product, with one participant experiencing LFT elevation above normal limits. All three received a tapering course of corticosteroids. As of May 7, 2018, none of these participants experienced a bleed, but Participant 13 received an infusion to treat a rolled left ankle.

Preliminary *SPK-8011* Phase 1/2 data in hemophilia A: Clinical outcomes for first 4 participants demonstrated by near elimination of bleeds and infusions

100% reduction in mean ABR in first 4 participants beginning 4 weeks post-vector infusion (82% beginning at time of vector infusion)



98% reduction in mean AIR in first 4 participants beginning 4 weeks post-vector infusion (96% beginning at time of vector infusion)



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Note: *SPK-8011* data as of December 6, 2017; Dotted boxes denote AIR extrapolated from infusions.
**Participants 1 and 3 both received an infusion of factor for dental extraction procedures.

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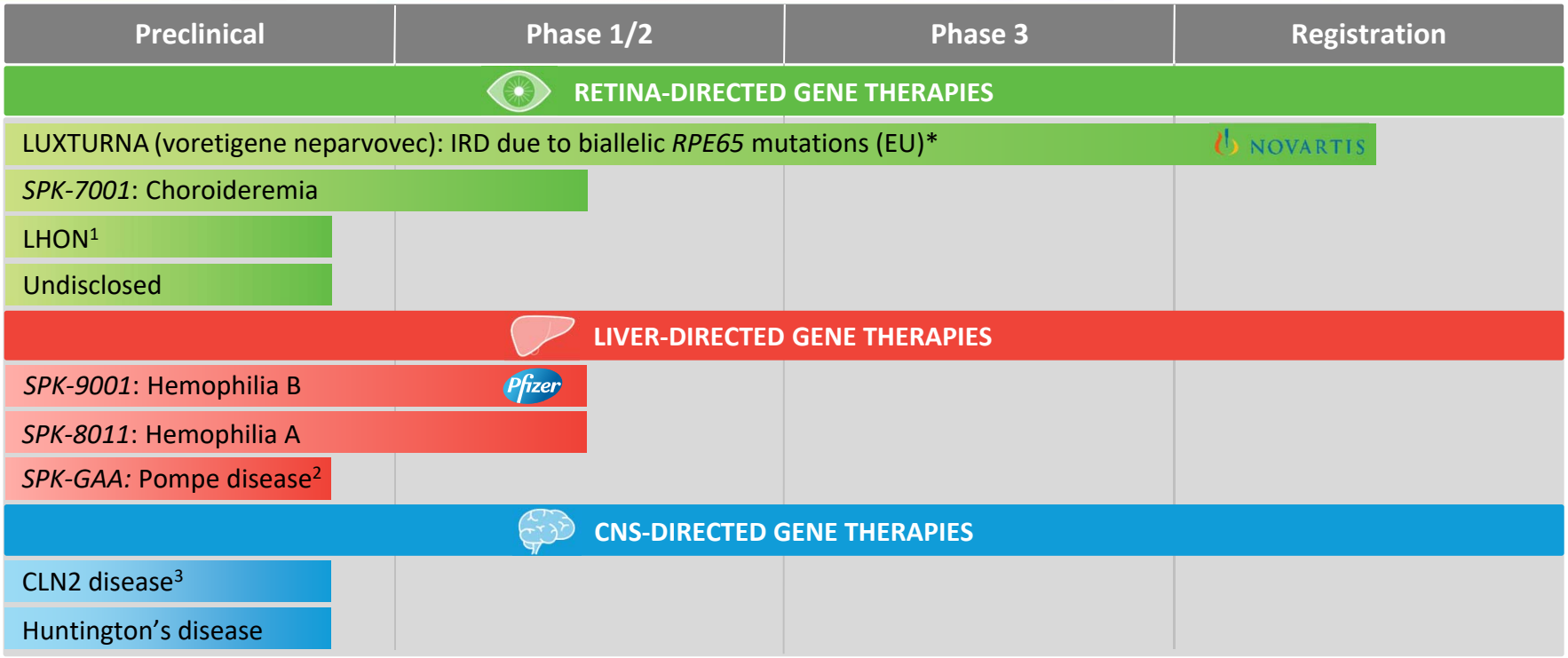
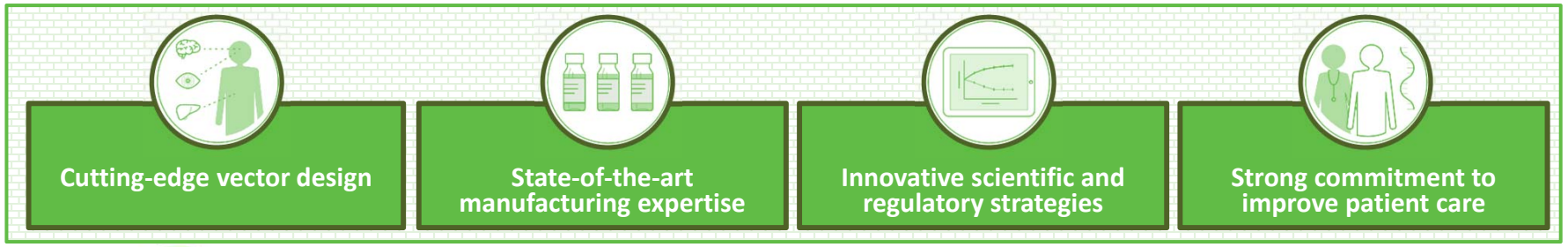
Fully-integrated AAV gene therapy platform and pipeline

Spark development pipeline

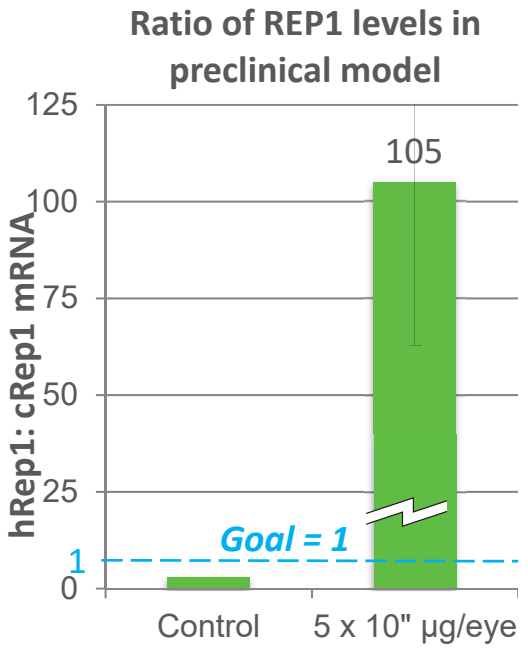




[1]Leber hereditary optic neuropathy; [2]Initial construct licensed from Genethon; [3]Form of Batten Disease.
*Approved in the US; MAA validated and under review in EU, with ex-US rights licensed to Novartis.

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**: Additional analyses of earlier- and later-stage disease cohorts to be conducted in 2018



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

Investigational *SPK-GAA* for Pompe disease: Optimized to address drawbacks of standard of care (SoC)

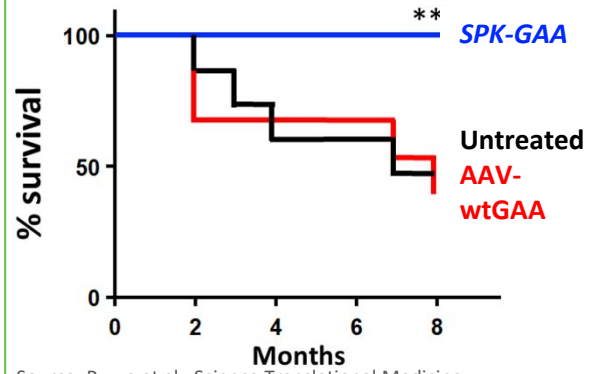
Shortcomings of current SoC: GAA enzyme replacement

- Replacement of recombinant form of missing enzyme (*wtGAA*) results in limited efficacy in many affected patients
- Lengthy (3-5 hours every 2 weeks) and costly infusions
- Potential for immunogenicity in some patients

SPK-GAA points of differentiation

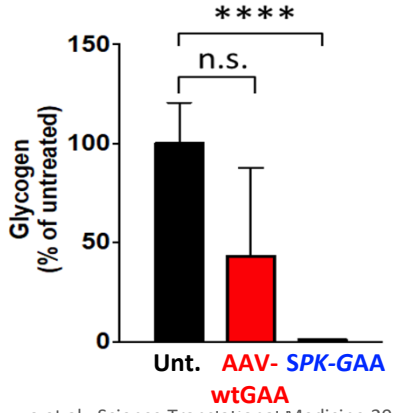
- Novel *GAA* transgene (licensed from Genethon) engineered for superior secretion and therapeutic effect
- Potential for greater glycogen clearance than ERT with AAV-mediated continuous elevation in *GAA* levels
- Evidence of reduced immunogenicity of secreted (vs. native) *GAA* in Pompe mice

SPK-GAA's secretable _GAA_ transgene expression results in superior rescue of Pompe mouse model vs. AAV-wtGAA



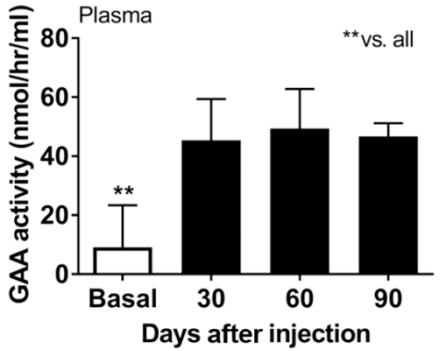
Source: Puzzo et al., Science Translational Medicine 2017 and unpublished results

SPK-GAA gene transfer in Pompe mouse model results in superior clearance of glycogen from muscle



Source: Puzzo et al., Science Translational Medicine 2017

GAA activity levels observed in NHP plasma at _SPK-GAA_ dose of $2x10^{12}$ vg/kg (levels therapeutic in mouse model)



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

Next steps: **Complete IND-enabling** work in **2018**

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

**p<0.01, ****p<0.0001

Spark's AAV manufacturing facility is the first and only FDA-approved commercial AAV manufacturing facility in the US

Established manufacturing process and capabilities

- Purpose-built, multi-suite, **in-house cGMP facility approved by FDA** and recent **successful inspection by EMA**
- **In-house manufacturing** of worldwide commercial LUXTURNA supply **for Novartis and** initial Phase 3 *SPK-9001* 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

Processes currently being implemented

- Spark has achieved **proof-of-concept** in a fully scalable, serum-free **suspension cell culture system** utilizing our current HEK293 cell line
- **Ongoing scale-up and implementation** of new upstream and downstream processes
  - Leveraging **Brammer Bio** facilities and capabilities to execute on **Spark-developed process**
- **Scale-up** currently **tracking in-line** with plans to have suspension process support Hem A clinical supply needs

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

Designed to support anticipated requirements for Hemophilia A and other future potential products

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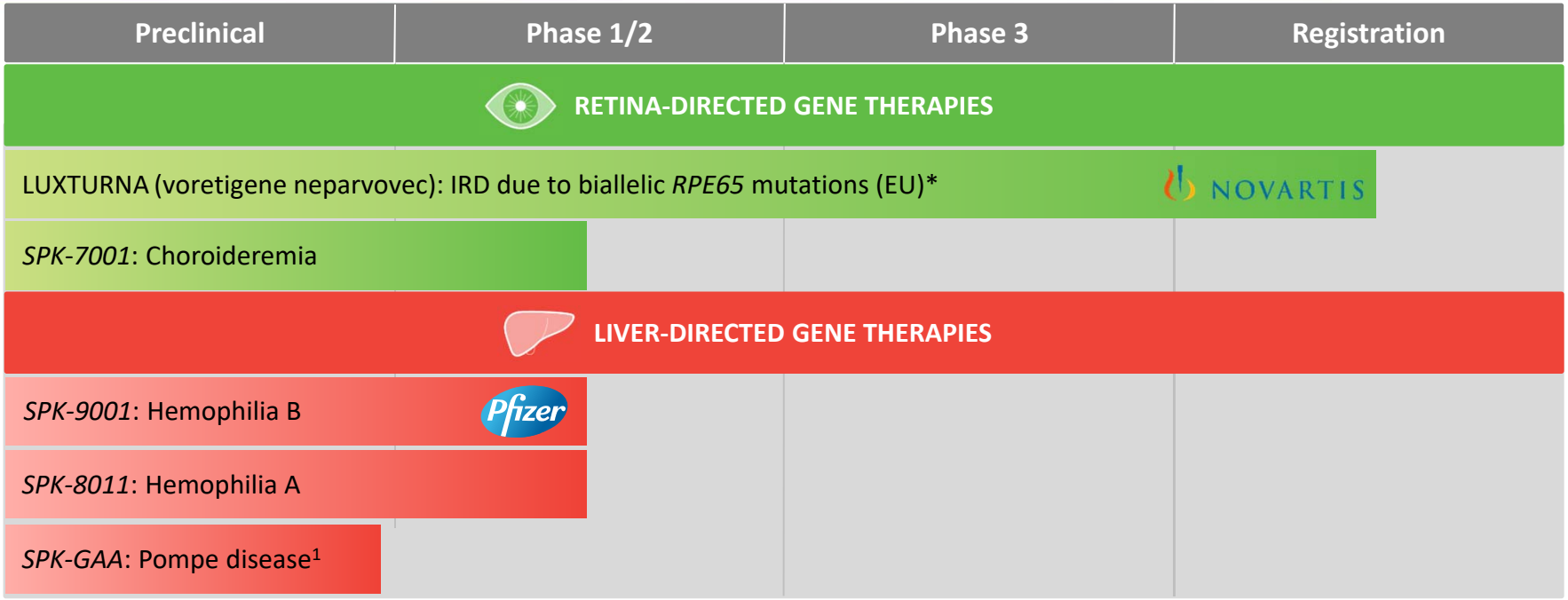
A catalyst rich 2018



Retina-directed gene therapy catalysts

- ✓ **January 2018:** Investigational LUXTURNA ex-US rights licensed to Novartis
- ✓ **End of 1Q18:** LUXTURNA available in the United States
- ✓ **1Q18:** First patients treated
- ✓ **2Q18:** Sale of priority review voucher
- ● **3Q18:** LUXTURNA regulatory action by EMA
- ● **2H18:** Update on maturing *SPK-7001* dataset

Liver-directed gene therapy catalysts

- ✓ **1Q18:** Completed enrollment of additional *SPK-9001* Phase 1/2 participants
- ✓ **May 2018:** Updated on additional *SPK-9001* Phase 1/2 participants treated with all-column downstream material
- ● **Mid-year:** Complete transition of *SPK-9001* to Pfizer to enable Phase 3 initiation
- ● **3Q18:** *SPK-8011* Phase 1/2 clinical data update
- ● **2018:** Complete IND-enabling studies for *SPK-GAA* for Pompe

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