MVA-BN dose sparing

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- If MVA-BN need exceeds supplies, what options exist?
  - Use ACAM2000
    - Not approved for monkeypox
    - Risk (myocarditis and pericarditis, encephalomyelitis, progressive vaccinia, generalized vaccinia, ocular complications, etc.
  - Extend supply of MVA-BN by using less vaccine

MVA-BN (JYNNEOS) licensed based on vaccinia-specific GMT being non-inferior to ACAM2000

- Plus supporting NHP Monkeypox model at 1x10^8

ACAM2000 was licensed based on vaccinia-specific GMT non-inferiority to Dryvax

	MVA-BN (N=185)			ACAM2000 (N=186)			Ratio of GMTs MVA/ ACAM		Non-Inferiority (Yes/No)
Visit Week	n	GMT	95% CI	n	GMT	95% CI	Ratio	95% CI	
Plaque Reduction Neutralization Test									
Week 0	185	1.0	[1.0, 1.1]	186	1.0	[1.0, 1.0]	1.008	[0.97, 1.05]	-
Week 2	184	16.2	[13.0, 20.1]	184	16.2	[13.1, 20.0]	0.997	[0.74, 1.35]	-
Week 4	185	16.9	[13.7, 20.8]	186	79.3	[67.1, 93.8]	0.213	[0.16, 0.28]	-
Week 6	185	153.5	[134.3, 175.6]	181	64.7	[54.9, 76.2]	2.372	[1.92, 2.93]	-
Peak Visit	185	**153.5**	[134.3, 175.6]	186	**79.3**	[67.1, 93.8]	**1.935**	**[1.56, 2.40]**	Yes

Prespecified noninferiority required the 95% CI of GMT ratio MVA:ACAM2000 to be above 0.5.

FDA Summary Basis for Regulatory Action (https://www.fda.gov/media/131802/download)
Pittman et al, NEJM 2019

Approaches to evaluate lower dose

- Efficacy
  - For an effective vaccine with few events, non-inferiority trial will be very large
  - Right now, we don't have enough information for sample size calculations

- Immunogenicity
  - Threshold
    - We don't know what GMT is correlated with protection for monkeypox
    - Vaccinia PRNT GMT of 32 correlated with prevention of smallpox *(Mack et al, Am J Trop Med Hyg 1972)*
      - How much confidence should we have extrapolating smallpox GMT correlates for dryvax to monkeypox efficacy with MVA-BN
  - Non-inferiority
    - Compared to ACAM2000
      - Risk of ACAM2000
    - Compared to MVA-BN
      - NI to MVA-BN titers
      - NI using MVA-BN and calculating back to ACAM2000 titers

Dose Sparing – reduced dose

	MVA-BN formulation	1 X10^7 $TCID_{50}$	2 X10^7 $TCID_{50}$	5 X10^7 $TCID_{50}$	1 X10^8 $TCID_{50}$	Assay
Vollmar et al, Vaccine 2006	Liquid	6.4	--	--	29.3	IHD-J PRNT GMT
Frey at al. Vaccine 2007	Lyophilized	--	347.2 (161.9, 744.7)	551.5 (321.5, 946.0)	914.5 (528.0, 1584)	MVA PRNT GMT
von Krempelhuber et al. Vaccine 2010	Lyophilized	--	5.5 (3.2, 9.6)	10.3 (5.8, 18.4)	19.4 (11.1, 34.2)	IHD-J PRNT GMT

5x10^7 GMT may be near ACAM2000.

Lower doses subcutaneously are likely to be inferior to ACAM2000

Dose Sparing – 1 dose

	MVA-BN (N=185)			ACAM2000 (N=186)			Ratio of GMTs MVA/ ACAM		Non-Inferiority (Yes/No)
Visit Week	n	GMT	95% CI	n	GMT	95% CI	Ratio	95% CI	
Plaque Reduction Neutralization Test									
Week 0	185	1.0	[1.0, 1.1]	186	1.0	[1.0, 1.0]	1.008	[0.97, 1.05]	-
Week 2	184	16.2	[13.0, 20.1]	184	16.2	[13.1, 20.0]	0.997	[0.74, 1.35]	-
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Pittman et al, NEJM 2019

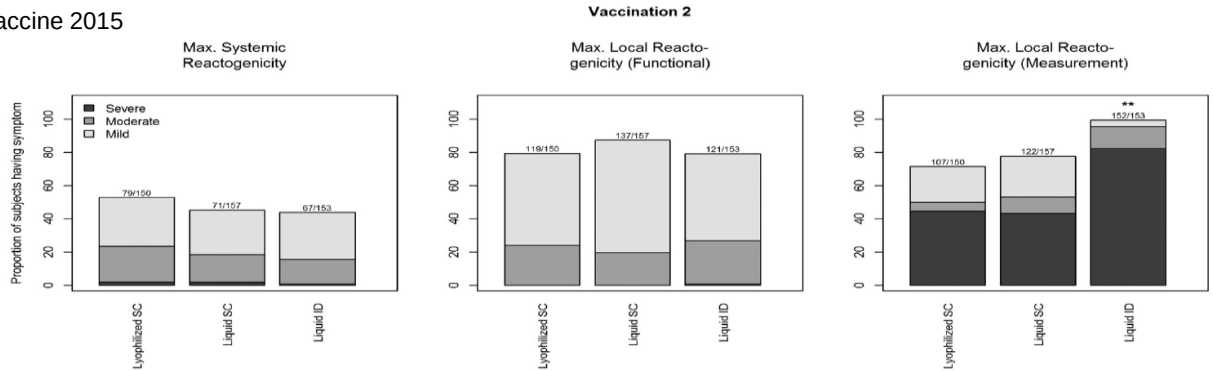
1 dose is likely to have lower GMT compared to 2 doses
There is other support for 1 dose:
- Dryvax demonstrated efficacy within 2 weeks of vaccination
- MVA-BN has similar titers to ACAM2000 at 2 weeks; ACAM2000 has similar titers to Dryvax
- 1 dose in NHP model protected against mortality and decreased lesion count.

Several locales have started using 1 dose strategy (second dose if able)

Dose Sparing - intradermal

Study visit day	Group		
	Lyophilized SC1x10^8 N=145 GMT [95% CI]	Liquid SC 1x10^8 N=149 GMT [95% CI]	Liquid ID 2x10^7 N=146 GMT [95% CI]
Day 0	7.5 [,]	7.7 [7.4, 8.0]	7.7 [7.4, 7.9]
Day 14	10.9 [9.9, 12.0]	10.0 [9.0, 11.1]	10.3 [9.3, 11.3]
Day 28	10.8 [9.9, 11.9]	9.6 [8.7, 10.6]	10.8 [9.9, 11.9]
Day 42	77.6 [62.3, 96.7]	45.2 [36.4, 56.2]	54.4 [43.7, 67.8]
Peak post vaccination 2	87.8 [71.2, 108.3]	**49.5 [40.0, 61.3]**	**59.6 [48.1, 74.0]**

Frey et al, Vaccine 2015



Downside to intradermal
- not as easy to administer (though is done for Tuberculin skin test)
- will have increased erythema/induration

NIAID Dose Sparing Trial (still in development)

- Immunogenicity trial
- Healthy volunteer including at risk groups
- 3 arms:
  - Arm 1: MVA-BN 2 x 10^7 ID (1/5th dose) on Days 1, 29
  - Arm 2: MVA-BN 1 x 10^8 SC on Days 1
  - Arm 3: MVA-BN 1 x 10^8 SC (licensed dose) on Days 1, 29
- Analyses
  - Compare ID 2-dose vs SC 1-dose.
    - to understand trade off of reactogenicity and immunogenicity.
  - Compare to standard dose
    - NI to MVA-BN that will be above ACAM2000 GMT.

Conclusions

- Trials to extend MVA-BN doses are needed.
  - Dose sparing may not be needed, but we should ensure we have the data.

- 1-dose subcutaneous (at standard dose) and 2-dose intradermal (at reduced dose) regimens may be beneficial.
  - Need to understand reactogenicity and immunogenicity of these approaches.

- This trial and other supporting data (discussed during this meeting) will inform potential efficacy trials.