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Ad26COV2.S Vaccine Janssen

ACIP Presentation

14 April 2021

Agenda

1. Company Statement for thrombosis (particularly CVST) with thrombocytopenia
2. Relevant Janssen clinical and post authorization data
3. Background Epidemiological data

Company Statement for thrombosis (particularly CVST) with thrombocytopenia

- *The safety and well-being of the people who use our products is our number one priority. While causality has not been fully established between these very rare events and our vaccine, we recognize these events could represent an important potential risk with Janssen vaccine. We are in the process of updating our CCDS and working with Health Authorities to update our labeling appropriately. J&J will continue to monitor this potential risk and is committed to efforts to ensure vaccinee and HCP awareness of important signs and symptoms, as well as appropriate diagnosis and management.*

Review of Janssen vaccine data

Janssen Phase III Pivotal Trial

Study 3001 – Venous Thrombosis Events (N=43,783 vaccinated)

TSFAE_VTE_COV3001: Study 3001 AEs				
	All AEs			
	Number of Cases up to 28 Days after Vaccination		Total Number of Cases	
	Ad26.COV2.S	Placebo	Ad26.COV2.S	Placebo
DVT	4 [c]	2	11	3 [a]
PE	2	1	8	4[a]
CVST	1 [b]	0	1	1
Venous thrombosis limb	1	0	1	0
embolism venous	0	0	1	0

[a] One individual in placebo experienced both DVT and PE: This individual had a SARS-CoV-2 PCR (+) nasal swab 4 days after th thrombosis

[b] Only one participant on Ad26 had low platelets (CVST)

[c] A second individual in Ad26.COV2.S group had multiple SARS-CoV-2 PCR (+) nasal swabs in the 2 weeks preceding the DVT.

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Source: Janssen clinical trial database

Janssen Phase III Two-Dose Pivotal Trial

Study 3009 – Venous Thrombosis Events (N=28,277 vaccinated)

TSFAE_VTE_COV3009: Study 3009 AEs (2 Dose Trial): Ongoing Blinded

	All AEs	
	Number of Cases up to 28 Days after Vaccination	Total Number of Cases
DVT	0	2
PE	1	4
CVST	0	0

[TSFAE_VTE_COV3009.RTF]
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No CVSTs observed with Janssen adenovirus vaccine program in Ebola and RSV

Source: Janssen clinical trial database

Sisonke Open Label Study in South African HCPs (N=272,438)

As of 09 Apr 2021:

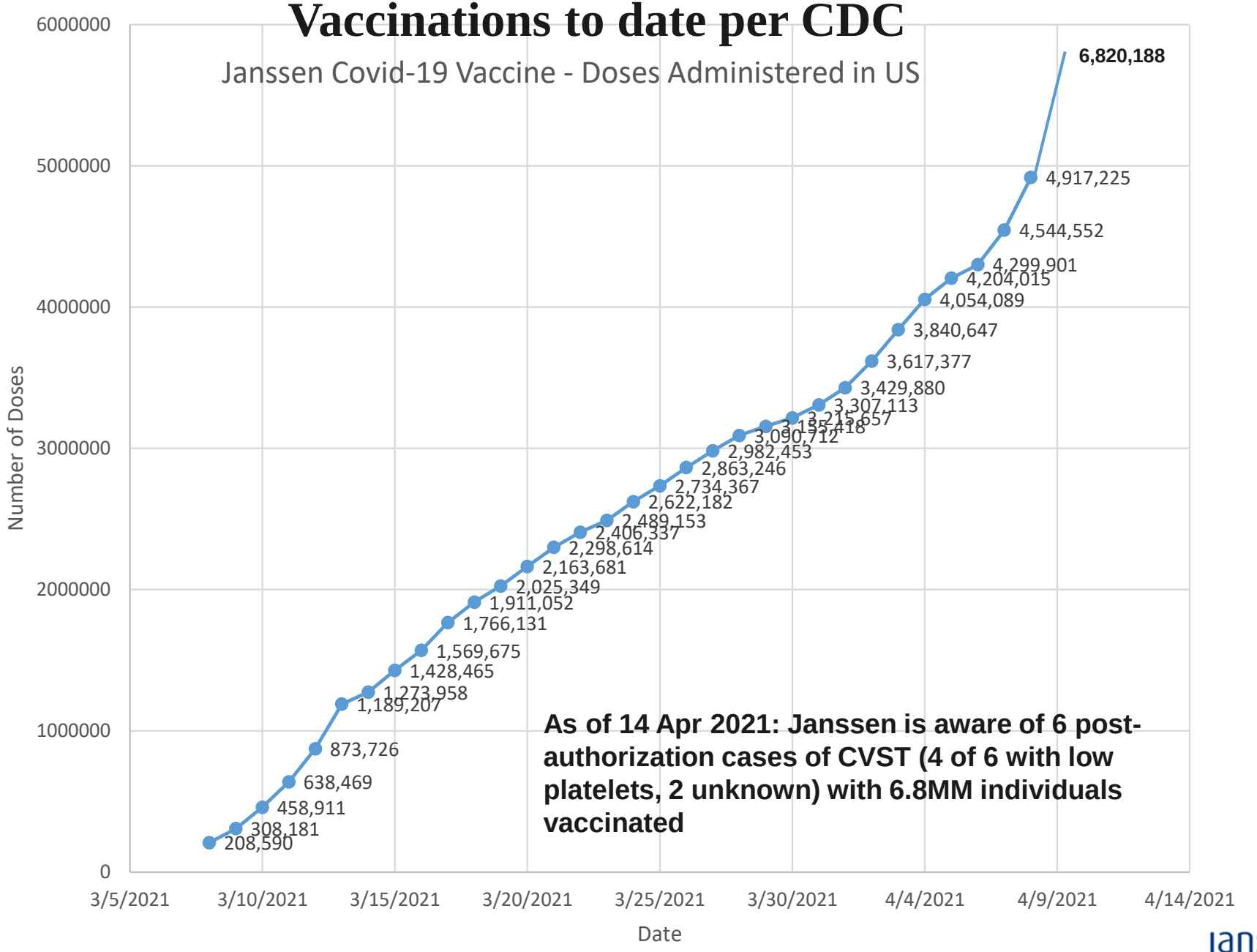
- No CVST cases reported
- One case of PE (no information on platelet or covid status)
- One case of CVA (age: 38 years old, female, 8 days after vaccination) - we are actively seeking additional information on this case
- One case of retinal vein thrombosis (age: 68 years old, diabetic, platelet count normal)

Source: Safety Reporting process - Sisonke Study team

All known cases of CVST and all known cases of thrombosis with thrombocytopenia with Janssen COVID vaccine

-summary table on next slide
-further individual case details can be found in the appendix section

Vaccinations to date per CDC



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As of 14 Apr 2021

SOURCE	CASE	CIOMS #	SERIOUS ADVERSE EVENT	RISK FACTOR(S)	PLATELET COUNT	COVID STATUS	TTO	Treatment	Status
CLINICAL TRIAL CASES									
Study 3001	25 YO Male on Vaccine	**20201017267**	CVST with hemorrhage	Stenosis of transverse sinus, URI suspected	64,000 (Anti-PF4+)	Negative	8 days	Heparin TPA and platelets, angioplasty and thrombectomies	Recovered
Study 3001	24 YO female on **placebo**	**20210202793**	CVST	Newly prescribed OCP	Normal (Anti-PF4-)	Negative	>50 days	N/A	Recovered
POST-AUTHORIZATION CASES									
VAERS # 1114806	45 YO female	**20210354798**	CVST with hemorrhage	none	"thrombocytopenia"	Unknown	11 days	Unknown	Fatal
VAERS 1133212	38 YO female	**20210408478**	CVST	Unknown	Unknown	Unknown	10-14 days	Heparin	Not Recovered at this time
VAERS #1141160-1	59 YO Female	**20210407977**	Extensive DVTs	Coronary artery disease	15,000	Unknown	7 days	Vena cava filter-IVC, thrombectomy	Not Recovered at this time
Janssen SAE Nevada	18 YO female	**20210407314**	CVST with hemorrhage	unknown	16,000	Unknown	14 days	Heparin then switched to "British guidelines" and thrombectomy	Not Recovered at this time
Janssen SAE (NEJM -editor notification) Nebraska	48 YO female	**20210415297**	TTP, splanchnic veins thrombosis, CVST, then given heparin and then additional hepatic and splanchnic vein thrombosis	Unknown	<13,000 (hi d-dimer, Anti-PF4+)	Negative	14 days	Heparin first and switched to argatroban then IVIG	Not Recovered at this time
Janssen SAE NJ/PA	26 YO female	**20210416236**	CVST, PE, portal vein thrombosis	Obesity	120,000 (hi d-dimer, Anti-PF4+)	Negative	7 days	Heparin and then IVIG	Discharged from hospital
VAERS 1182133	28 YO female	**In processing**	Details pending, FOI requested						

New England Journal Case (pre-publication of U of Nebraska case)

Received Thursday 08 Apr 2021

- 48-year-old woman with unremarkable past medical history to ER after 3 days of malaise and abdominal pain.

- Initial evaluation:
  - Mild anemia and severe thrombocytopenia (platelet count 13K) / Smear confirmed marked reduction in platelet count with occasional schistocytes.
  - Hypofibrinogenemia (89 mg/dL); prolonged aPTT (41 sec); markedly elevated D-Dimer.
  - Extensive splanchnic vein thrombosis on CT

- Transferred to reporting institution, with further evaluation and progression of thrombosis on heparin:
  - SARS-CoV2 RNA was not detected by RT-PCR
  - Head CT (for new-onset headaches) showed cerebral venous sinus thrombosis
  - Thrombosis progressed with hemorrhagic stroke despite treatment with heparin
  - Repeat CT angiography showed new thrombus involving right hepatic and splenic veins.
  - Further inquiry revealed patient received the Ad26.COV2.S vaccine 14 days before symptom onset.

- Evidence and management of possible Immune Thrombotic Thrombocytopenia (ITT):
  - Positive anti-PF4/heparin antibodies by ELISA (3.179 OD) - latex-enhanced immunoassay was negative
  - Heparin switched to argatroban
  - IVIG 1 gm/kg × 2 day
  - Platelet count increase from 30,000 to 145,000 over 5 days.
  - She remains critically ill at last report.

Direct Report to Janssen, CIOMS # 20210416236

Follow up phone contact with physician Monday, 12 Apr 2021

- 26-year-old woman, overweight but active, with no history of clotting disorder and on no medication.

- Initial presentation to ER:
  - Severe headache approximately 1 week following vaccination
  - Discharged home from ER with paracetamol and Benadryl
  - Headache persisted

- Subsequent hospital admission:

  - Hospitalized another week later for abdominal pain and rapid heart rate
  - Covid-19 infection “ruled out” (exact test unknown)
  - Laboratory evaluation revealed thrombocytopenia (platelet 120K), elevated D-Dimer (level unknow) and normal fibrinogen (level unknown)
  - Diagnostic scan showed CVST, portal vein thrombosis and PE
  - Initially treated with heparin, switched to IVIG after positive anti-PF4 antibodies result (level 3.0)
  - Platelet count reportedly started to increase prior to IVIG

- Patient discharged home on oral anticoagulant after 1-1.5 weeks in hospital

Clinical Trial (study 3001) Case CIOMS #20201017267

- Healthy 25 year-old male vaccinated on 9/21/2020
- 8 days post-vaccination: feeling progressively unwell, incl. fatigue, faintness, nausea and headache. Took NSAIDs
- 11 days post-vaccination: continued fatigue, weakness, nausea; developed abdominal pain and headache; Covid-19 swab negative
- Hospitalized 19 days post-vaccination (10/9/2020) after visual disturbance and passing out:
  - Laboratory evaluation: Platelet count was 64K; PT 17.7, INR 1.46; fibrinogen 154, wbc 12.4, hgb 12.7, and hct 36.1
  - CT/MRI/venogram: CVST and secondary cerebral haemorrhage
  - Underwent repeated cerebral vascular sinus thrombectomy/venoplasty due to re-occlusion, and noted to have stenosed cerebral sinus.
  - Also treated with low-molecular weight heparin and IV TPA
- Extensive haematology and infectious disease laboratory evaluation showed inclusive results. Patient discharged on treatment with apixaban
- Stored serum tested positive for anti-PF4 antibodies last week
- Recovery after repeat thrombectomy and balloon angioplasty procedures; epiglottitis while in hospital; discharge meds include apixiban

CVST Background Incidence Rates

- Published Literature from US and EU
  - ***Stam*** *et al. Thrombosis of the Cerebral Veins and Sinuses. N Engl J Med 2005; 352:1791-1798;* ***Janghorbani*** *M et al., Cerebral vein and dural sinus thrombosis in adults in Isfahan, Iran: frequency and seasonal variation. Acta Neurol Scand. 2008 Feb;117(2):117-21. doi: 10.1111/j.1600-0404.2007.00915.x. PMID: 18184347. ;* ***Bousser*** *MG, Ferro JM. Cerebral venous thrombosis: an update. Lancet Neurol. 2007 Feb;6(2):162-70. doi: 10.1016/S1474-4422(07)70029-7. PMID: 17239803.;* ***Coutinho*** *J.M et al, the incidence of cerebral venous thrombosis a cross sectional study, Stroke (2012);* ***Devasagayam*** *S et al. Cerebral Venous Sinus Thrombosis Incidence Is Higher Than Previously Thought: A Retrospective Population-Based Study. Stroke. 2016 Sep;47(9):2180-2. doi: 10.1161/STROKEAHA.116.013617. Epub 2016 Jul 19. PMID: 27435401.*

- Janssen Analysis of US healthcare claims and EHR databases
  - meta-analysis across 4 large US healthcare claims and 1 US EHR databases. Persons observed for at least 365 days prior to 1 January in 2017-2019 were included to generate incidence of the outcome ‘cranial venous sinus thrombosis’.
  - Methods are similar to those used in the multi-national network cohort study of 15 AESIs shared with FDA and EMA [Xintong et al., Characterizing the incidence of adverse events of special interest for COVID-19 vaccines across 8 countries: a multinational network cohort study. Manuscript under review: https://www.medrxiv.org/content/10.1101/2021.03.25.21254315v1]
  - All specifications and output for this analysis of CVST conducted by JNJ is stored in https://epi.jnj.com//atlas/#/iranalysis/548/.

CVST background incidence rates

Data source	Year of publication	Age group (in years)	IR (95%CI) in 100,000 person-years	
US claims and EHR databases (Janssen internal access)	2021		Male	Female
		18-34	1.70 (0.02-145.10)	2.64 (0.25- 28.29
		35-54	0.92 (0.13- 6.63)	1.90 (0.19-19.43)
		55-64	0.84 (0.06-11.04)	1.10 (0.06-20.62)
		65-74	1.58(0.11-21.63)	0.8 (0.11- 5.67)
		75-84	1.14(0.37-3.45)	1.25 (0.02-65.54)
		85+	1.26 (0.00-425.37)	1.33 (0.08-23.12)
		Overall (18-85+)	1.23 (0.1- 56.53)	1.75 (0.16-23.19)
ACCESS - FISABIO	2021		All genders	
		0-19	0.12 (0.05-0.29)	
		20-29	0.25 (0.10-0.60)	
		30-39	0.26 (0.12-0.55)	
		40-49	0.42 (0.25-0.71)	
		50-59	0.41 (0.23-0.72)	
		60-69	0.69 (0.42-1.13)	
		70-79	0.60 (0.33-1.08)	
		80+	1.08 (0.63-1.86)	
		Overall (year 2019)	0.48 (0.32-0.71)	
ACCESS – ARS IT	2021	0-19	0.34 (0.15-0.76)	
		20-29	0.64 (0.29-1.42)	
		30-39	1.71 (1.09-2.68)	
		40-49	1.88 (1.32-2.67)	
		50-59	1.00 (0.62-1.61)	
		60-69	1.29 (0.81-2.05)	
		70-79	1.91 (1.28-2.85)	
		80+	1.55 (0.93-2.57)	
		Overall (year 2019)	1.44 (1.08-1.92)	
Stam, 2005; Bousser, 2007	2005-2007	Overall (adults)	0.2-0.5 (NA)	
Janghorbani, 2008	2008	Overall (adults)	1.23 (NA)	
Coutinho, 2012	2012	Overall (adults)	1.32 (NA)	
Devasagayam, 2016	2016	Overall (adults)	1.57 (NA)	

- **Ongoing review of internal & publicly available data**

-Evolving literature on relationship between COVID and thrombocytopenic and thrombotic events

- Case reports of association between thromboembolic events including CVST with ITP and TTP

- US VAERS data on thrombocytopenic and thrombotic events (and other AESIs) for all available vaccines

- European EUDRAVIGILANCE data