

BLA 125518

Talimogene laherparepvec

FDA Presentation
Combined CTGTAC and ODAC Meeting
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Outline

- **Robert Le, MD, PhD**
 - Product information
 - Proposed indication
 - Background, current therapies for advanced melanoma
 - Phase 3 Study 005/05
 - Efficacy results
- **Abigail Luo, PhD**
 - Statistical review focusing on overall survival
- **Maura O’Leary, MD**
 - Safety results
- **Ramjay Vatsan, PhD**
 - Shedding data and proposed postmarketing study
 - Summary of review issues

Product Information

- **Talimogene laherparepvec: an attenuated herpes simplex virus type 1 engineered to express hGM-CSF**
- **Proposed mechanism of action:**
 - **direct oncolytic effect in injected lesions by replication of the virus in tumor cells resulting in their lysis**
 - **systemic anti-tumor immune response enhanced by the local expression of GM-CSF**

Proposed Indication

- **Talimogene laherparepvec is indicated for the treatment of injectable regionally or distantly metastatic melanoma.**
- **Primary basis of application: Study 005 / 05**

Melanoma

- 76,100 new cases and 9,710 deaths in the U.S. in 2014.
- Stage at diagnosis is the strongest predictive factor for survival

AJCC Stage	Clinical Status	5-year survival (%)
IIIA	1 lymph node	65-70
IIIB	1-3 involved nodes + ulceration	40-60
IIIC	1-3 nodes + nodal macrometastasis + ulceration	20- 35
IVM1a	Distant skin, nodal	30
IVM1b	Lung	20
IVM1c	Other visceral	5-10

Therapies for Advanced Melanoma

- **Surgery if feasible**
- **Radiation therapy if indicated**
- **Chemotherapy: dacarbazine (1975)**
- **Biologic therapies:**
 - IL-2 (1998), ipilimumab (2011)**
 - nivolumab (2014), pembrolizumab (2014)**
- **Targeted therapies:**
 - vemurafenib (2011), dabrafenib (2013)**
 - tremetinib (2013)**

Trial Design:

Phase 3 Study 005/05

- **Randomized (2:1) open-label multicenter international study: talimogene laherparepvec vs control (GM-CSF).**
- **Special Protocol Assessment (SPA) agreement in 2008.**
- **Stage IIIB, IIIC, or IV unresectable melanoma suitable for direct injection with at least 1 injectable lesion ≥ 10 mm in longest diameter or multiple lesions totaling ≥ 10 mm.**
- **Subjects were eligible based on stage at enrollment (not at initial diagnosis).**
- **Endpoints:**
 - **Primary: Durable Response Rate (DRR): complete response (CR) or partial response (PR) maintained for at least 6 months), determined by an Endpoint Adjudication Committee (EAC)**
 - **Secondary: overall survival (OS), best overall response, disease burden, duration of response, time to treatment failure (TTF).**

Dosing Regimen

Talimogene laherparepvec arm: injections into cutaneous, subcutaneous, and nodal lesions.

- **Initial dose is up to 4 mL of 10^6 plaque forming units (PFU)/mL**
- **Followed by 4 mL of 10^8 PFU/mL administered 3 weeks later;**
- **Subsequent doses of 4 mL of 10^8 PFU/mL administered every 2 weeks.**
- **Accelerated dosing: If any injected lesion(s) progressed, the injection frequency could increased to once per week for 4 weeks; may repeat X 3**

Control (GM-CSF) arm: 125 $\mu\text{g}/\text{m}^2/\text{day}$ SC for 14 days and off 14 days with each cycle

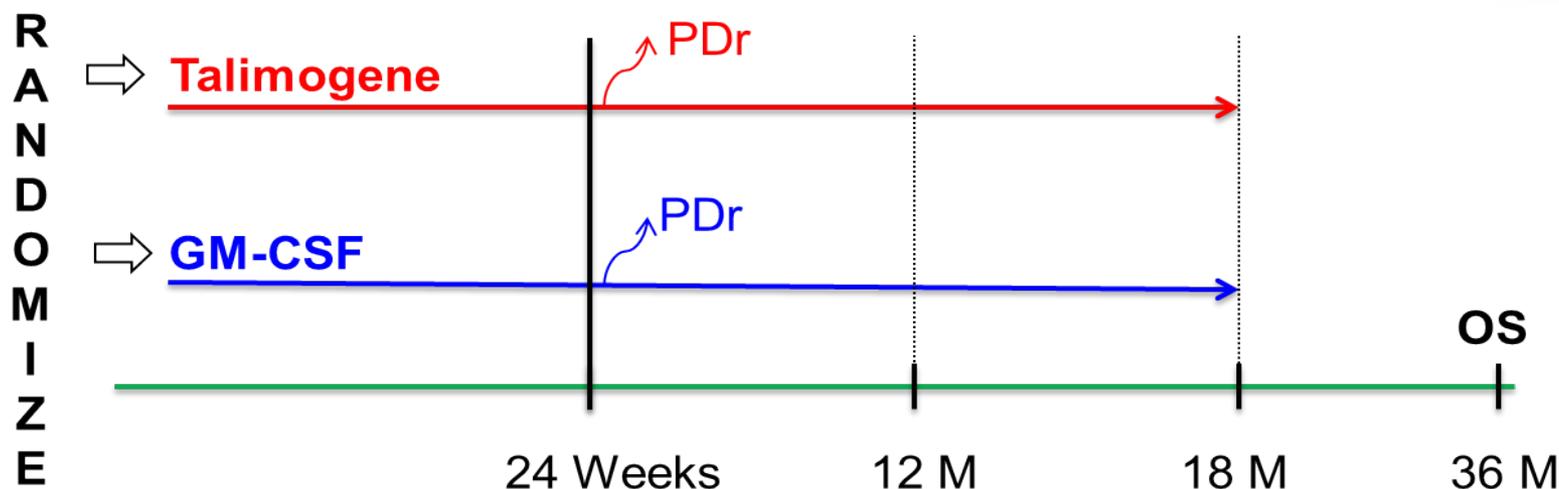
Dose Volume per Lesion

The volume of talimogene laherparepvec to be injected into each lesion was dependent on the size of the lesion

Lesion size (longest dimension)	Talimogene laherparepvec injection volume	Dose [concentration: 10 ⁶ PFU/mL]	Dose [concentration: 10 ⁸ PFU/mL]
> 5 cm	up to 4 mL	up to 4 million PFU	up to 400 million PFU
> 2.5 cm to 5 cm	up to 2 mL	up to 2 million PFU	up to 200 million PFU
> 1.5 cm to 2.5 cm	up to 1 mL	up to 1 million PFU	up to 100 million PFU
> 0.5 cm to 1.5 cm	up to 0.5 mL	up to 500,000 PFU	up to 50 million PFU
≤ 0.5 cm	up to 0.1 mL	up to 100,000 PFU	up to 10 million PFU

Maximum injection volume for each treatment visit: 4 mL

Treatment Plan and Follow-up



- Subjects received treatment until week 24 (even in the presence of PD).
- After 24 weeks, subjects remained on study until clinically relevant disease progression (PDr = disease progression associated with a decline in performance status and/or alternative therapy was required in the opinion of the investigator), up to 12 months.
- Subjects in response at 12 months continued treatment for up 18 months.
- Subjects were to be followed for OS for at least 36 months.

Patient Assessments

- **Clinical evaluation every 4 weeks**
- **CT scans every 12 weeks**
- **Ultrasonograms of nodal or other soft tissue masses every 12 weeks if indicated**
- **MRI of brain every 16 weeks**
- **PET or PET/CT scans of whole body at screening and for subjects who reached 9 months of therapy**

Response Assessment

- **Lesion response categorized as CR, PR, SD or PD according to WHO tumor response criteria using bi-dimensional measurements.**
- **Overall melanoma response evaluation based on integrated assessments on all measurable lesions (present at baseline and new lesions appearing during treatment) and non-measurable but evaluable lesions.**
- **Only subjects who had reached > 9 months on treatment, or CR, or PR, as per investigators were subsequently evaluated by Endpoint Assessment Committee (EAC).**

Efficacy Results

Demographics and Disease Characteristics

	Talimogene laherparepvec (N = 295)	GM-CSF (Control) (N = 141)
Median age, years	63	64
Female gender	41%	45%
Race: Caucasian	98%	98%
ECOG PS 0	71%	69%
Disease stage at enrollment		
IIIB, IIIC	8%, 22%	9%, 22%
IV: M1a, M1b, M1c	25%, 22%, 23%	31%, 18%, 21%
LDH >ULN	5.1%	3.5%
BRAF status		
Mutation, Wild-type	15.6%, 15.3%	16.3%, 16.3%
Unknown or missing	69.2%	67.4%

Subject Disposition

	Talimogene laherparepvec N = 295 (%)	Control N = 141 (%)
Subjects who received treatment	291 (98.6%)	127 (90.1%)
Subjects who never received treatment	4 (1.4%)	14 (9.9%)

Cumulative Number of Subjects who Discontinued Treatment after Randomization

Treatment Arm	N	≤ 3 M	≤ 6 M	≤ 9 M	≤ 12 M	≤ 16 M	≤ 18 M
Talimogene laherparepvec	295	86 (29.2%)	172 (58.3%)	226 (76.6%)	266 (90.2%)	277 (93.9%)	291 (98.6%)
Control	141	79 (56.0%)	106 (75.2%)	111 (78.7%)	124 (87.9%)	125 (88.7%)	127 (90.1%)

Note: N = Number of subjects; M = Months

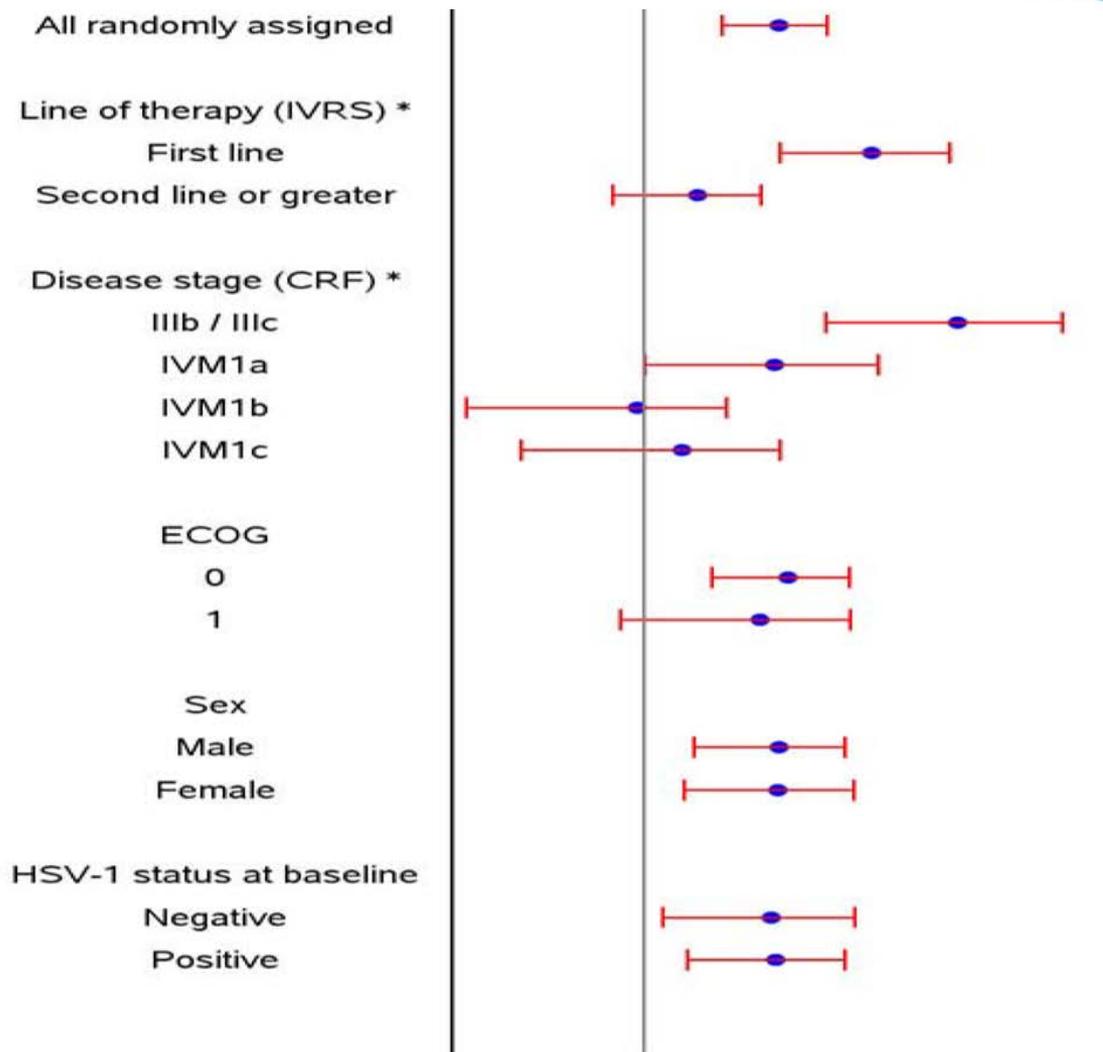
Primary Endpoint: Durable Response Rate Based on EAC Evaluation[#]

Talimogene laherparepvec N (%)	Control N (%)	Odds ratio (95% CI)
48 (16.3%)	3 (2.1%)	8.9 (2.7, 29.2) P < 0.0001

CI = confidence interval;

[#]EAC reviewed 19 subjects in control arm, and 124 subjects in talimogene laherparepvec arm.

Durable Response Rate: Subgroup Analysis (EAC)



DRR: % Difference (Talimogene laherparepvec Minus Control)

Uncertain Systemic Effects

- **FDA review of the responses in “uninjected lesions” raised several concerns.**
 - **Some lesions reported as uninjected appeared to be too small for reliable assessment.**
 - **It was difficult for FDA to determine which lesions were never injected.**

Study 005/05 did not collect immune response data to assess correlation with clinical outcomes.

Distribution of Subjects According to Size of the Largest Baseline Measurable Lesions

Largest Lesion Size at Baseline (cm ²)	Talimogene laherparepvec			Control		
	All (N=289)	Durable Responder (N=46)	Not Durable Responder (N=243)	All (N=127)	Durable Responder (N=2)	Not Durable Responder (N=125)
<0.5	12 (4.2%)	7 (15.2%)	5 (2.1%)	7 (5.5%)	0	7 (5.6%)
0.5 to (<1)	17 (5.9%)	7 (15.2%)	10 (4.1%)	6 (4.7%)	0	6 (4.8%)
1 to (<2)	34 (11.8%)	11 (23.9%)	23 (9.5%)	16 (12.6%)	0	16 (12.8%)
2 to 1164	226 (78.2%)	21 (45.7%)	205 (84.4%)	98 (77.2%)	2 (100%)	96 (76.8%)

- Recorded by Investigators in the ITT Population (by treatment arm and status of being durable responder)
- 3442 records of measurable lesions in 416 subjects

Primary Endpoint Summary

- **In this BLA, the primary evidence of effectiveness of talimogene laherparepvec comes from Study 005/05.**
- **In this randomized, Phase 3 study, subjects who received talimogene laherparepvec had a statistically significant higher durable response rate, including complete or partial response maintained for at least 6 months, compared with subjects who received control (GM-CSF).**

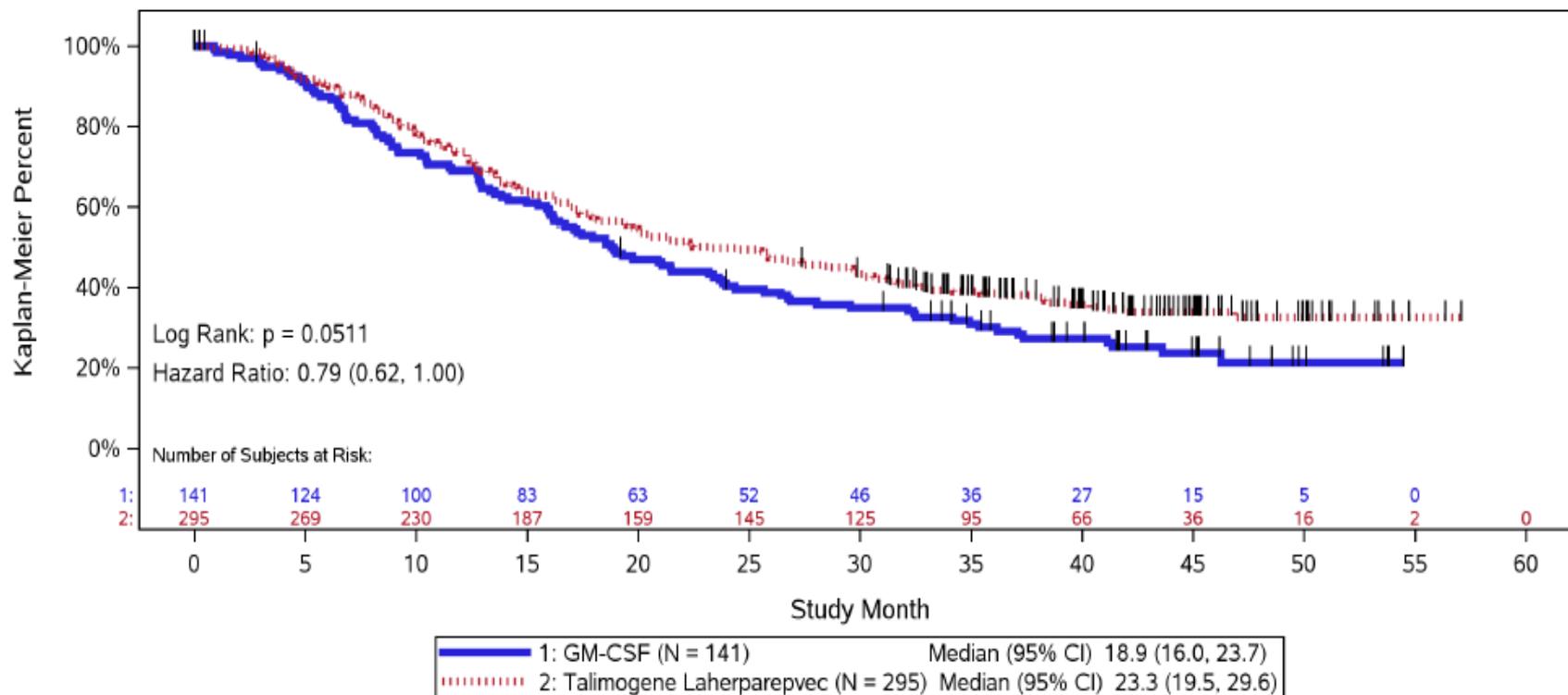
Durable Response Rate (DRR)

- **Randomize 430 subjects**
 - Targeting 360 evaluable for durable response
 - 90% power to detect 13% vs 3%, or 21% vs 8%
- **Plan for primary analysis**
 - Intent-to-treat, all randomized subjects
 - To occur after last randomized subject on study for 18 months
 - Fisher's exact test, $\alpha = 0.0488$, accounting for interim analyses
- **Study result**
 - Analysis cut-off date (ACOD): 12/21/2012
 - DRR: 16.3% vs. 2.1%
 - $p < 0.0001$
 - Unadjusted relative risk (95% CI) : 7.6 (2.6, 25.5)

Overall Survival (OS)

- **Plan for primary analysis**
 - Intent to treat, all randomized subjects
 - To occur after 290 deaths
 - Unstratified log-rank test, $\alpha = 0.05$
 - Final descriptive analysis after all subjects followed for 3y
- **Study result**
 - ACOD: 3/31/2014
 - 4.4 months improvement in median survival
 - $p = 0.051$
 - Final descriptive analysis (ACOD 8/5/2014) had one additional death in the talimogene arm

OS Primary Analysis: Survival Curve (ITT)



Source: Supplemental CSR Figure 14-4.1.1

- **Talimogene: Death 189/295 (64%), Censored 106/295 (36%)**
- **Control: Death 101/141 (72%), Censored 40/141 (28%)**

Overall Survival: Potentially Informative Censoring

- All subject were to be followed at 3 months intervals until End of Study.
- Randomized but not treated
 - talimogene laherparepvec: 4/295 (1.4%)
 - Control arm: 14/141 (9.9%)
- Reason for ending study among censored observations
 - Administrative censoring: ending because of ACOD
 - Potentially informative censoring: ending for other reasons

Potentially Informative Censoring (2)

Talimogene Laherparepvec 3/295 (1%)				Control 7/141 (5%)			
Subject #	Reason for Ending Study	Censoring Time (Primary Analysis)	Censoring* Time (FDA Sensitivity Analysis)	Subject #	Reason for Ending Study	Censoring Time (Primary Analysis)	Censoring* Time (FDA Sensitivity Analysis)
1	O	1	1226	1	CW	1	1449
2	CW	8	1072	2	CW	1	1014
3	CW	834	1341	3	CW	2	1573
				4	LFU	16	1496
				5	CW	86	1575
				6	CW	585	1744
				7	CW	730	1128

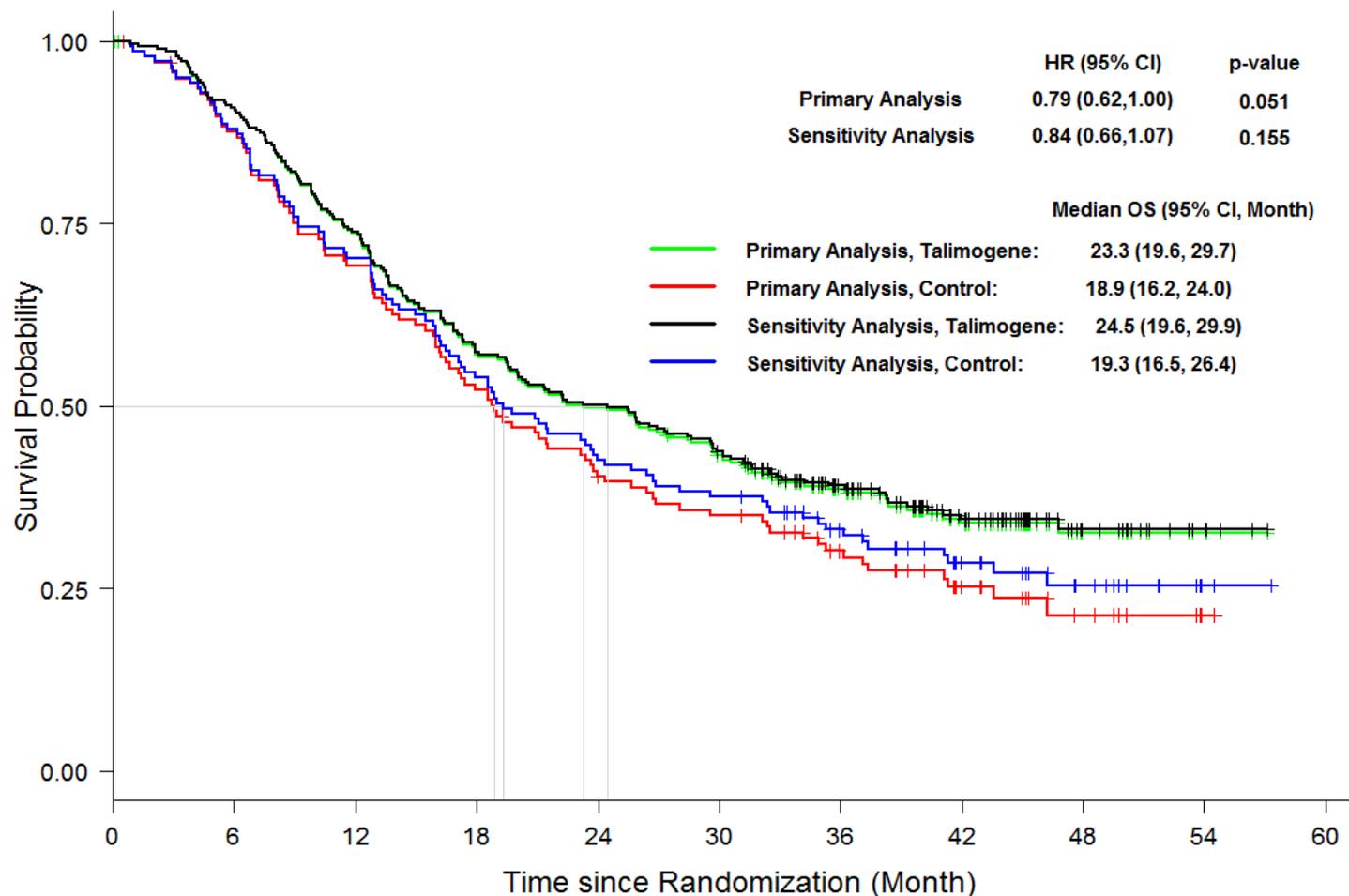
•*: The last column, under each study arm, shows the imputed censoring time using ACOD 3/31/2014, for the FDA post-hoc sensitivity analysis reported in the next slide.

•O: subject randomized in error; subject was ineligible [for enrollment] due to brain mets

•CW: consent withdrawn

•LFU: lost to follow-up

OS: Primary Analysis versus FDA Sensitivity Analysis



Source: FDA analysis



Safety Results

BLA Safety Databases

Primary Safety Database (Study 005/05):

- n= 127 GM-CSF, control
- n = 292 talimogene laherparepvec

Drug Exposure

	Talimogene Laherparepvec	Control
Subjects (n)	292	127
Treatment Exposure		
Accelerated Dosing (mean)	3.2x 10⁸ pfu/wk	
Standard Dosing (mean)	2.7 x 10⁸ pfu/bi-wk	
Treatment Duration		
Mean (weeks)	26.8	15.8
Standard Deviation (weeks)	18.4	15.8
Median (weeks)	23.0	10.0
Min, Max (weeks)	0.1, 78.9	0.6, 72.0

Frequent Treatment-Emergent Adverse Events ($\geq 25\%$ of Subjects in 005/05)

Treatment-Emergent Adverse Events (TEAEs)	Talimogene laherparepvec n=292 (%)	Control n=127 (%)
Any	290 (99.3%)	121(95.3%)
Fatigue	147 (50.3%)	46 (36.2%)
Chills	142 (48.6%)	11 (8.7 %)
Pyrexia	125 (42.8%)	11 (8.7%)
Nausea	104 (35.6%)	25 (19.7%)
Influenza-like Illness	89 (30.5%)	19 (15%)
Injection site pain	81 (27.7%)	8 (6.3%)

Death Events

- Overall there were 189 deaths on the talimogene laherparepvec arm for 005/05 and 101 for the GM-CSF arm while on therapy or in follow-up.
- 14 deaths within 30 days of last treatment including 2 on Study 005/05E for talimogene laherparepvec
- 12 deaths on the talimogene laherparepvec arm and two on the GM-CSF arm
- 9/12 for talimogene laherparepvec were due to PD.
- 3/12:
 - Myocardial infarction
 - Cardiac arrest
 - Sepsis

Adverse Events of Interest

Adverse Events of Special Interest	Talimogene laherparepvec n* = 292 (%)	Control n* = 127 (%)
Subjects reporting T-E AEs of Special Interest	275 (94.2%)	108 (85%)
Flu-like symptoms	264 (90.4)	83 (65.4)
Injection site reactions	122 (41.8)	64 (50.4)
Hypersensitivity	53 (18.2)	25 (19.7)
Cellulitis: injection site	18 (6.2)	2 (1.6)
Herpes simplex virus infection	16 (5.5)	2 (1.6)
Vitiligo	15 (5.1)	2 (1.6)

Adverse Events of Interest with Low Incidence in Talimogene Laherparepvec Arm

- Immune-mediated events (n=6)
 - Glomerulonephritis (n=2)
 - Interstitial pneumonitis, history of ulcerative colitis
 - Vasculitis
 - Exacerbation of pre-existing psoriasis
 - Hypothyroidism.
- Other Malignancies (n=7)
 - Plasmacytoma; history of smoldering MM
 - Metastatic squamous cell carcinoma
 - Adenocarcinoma of the lung
 - Transitional cell bladder cancer; n=2
 - Recurrence of prostate cancer
 - Squamous cell cancer of the skin.
 - Tonsillar neoplasm

Adverse Event of Interest

– Amputation

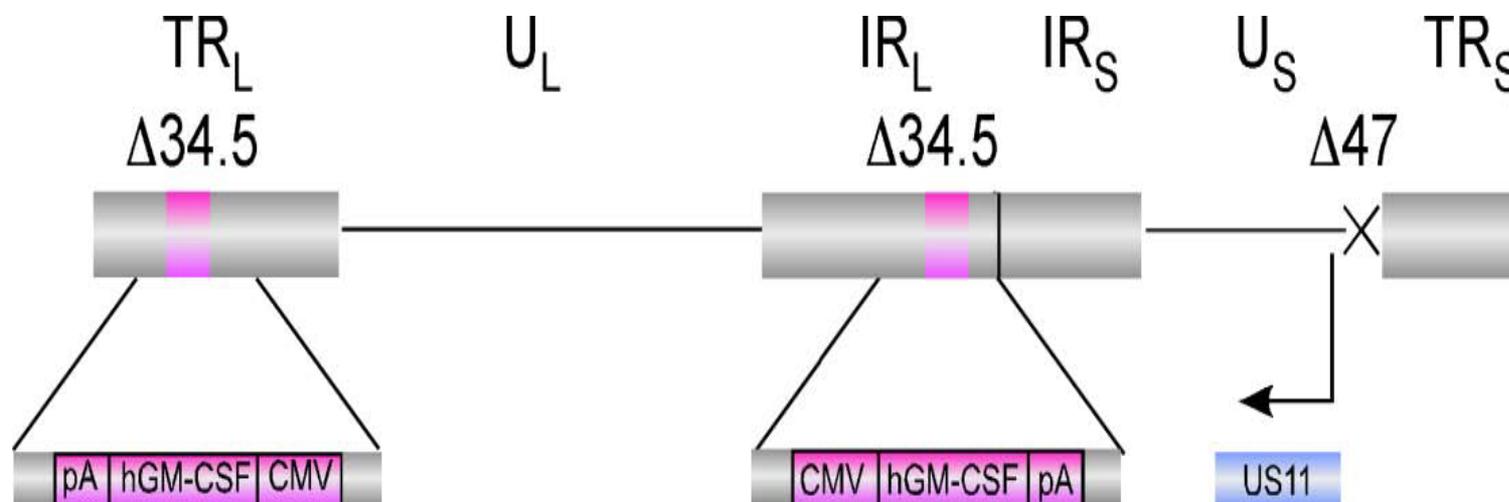
- Late occurrence of a serious adverse event.
 - Six months after last dose of talimogene laherparepvec in an 84 year old female.
- Durable responder
- Six months after completion of talimogene laherparepvec treatment
 - A below-the-knee amputation for a non-healing, infected wound.
- Prior to enrollment on 005/05, the subject had surgery and radiation to this area
- Talimogene laherparepvec was given in this area as therapy on 005/05

Accidental Exposure: Talimogene Laherparepvec

- Questionnaires for household contacts and health care professionals
- Compliance:
 - Household contacts: 49-55% / Medical Personnel 14%
- Results:
 - Herpetic whitlow lesion at site of needle puncture. Plaque assay 10 days later was positive, qPCR HSV-1 viral DNA
 - Resolved with acyclovir
 - Repeat needle puncture also responded to treatment
 - Third episode also treated without sequelae.
- Six sites reported spills of the talimogene laherparepvec.
- One eye exposure (Pharmacist), treated, no infection noted.
- Close contacts: no increased risk but follow-up limited.

Results from Ongoing Shedding Study and Proposed Postmarketing Study

Schematic of Genome of Talimogene Laherparepvec



- **GM-CSF cloned into viral ICP34.5 gene, interrupting gene expression**
 - ICP34.5 is associated with neurovirulence.
- **ICP47 gene is deleted**
 - ICP47 blocks antigen presentation, allowing wtHSV1 to escape immune surveillance
 - ICP 47 deletion also causes early expression of US11

Reasons for Shedding Studies

Talimogene laherparepvec is a replication competent HSV-1 virus:

- **Capable of amplification in vivo**
- **Can spread to uninjected tissues**
- **Can recombine with wild type HSV-1 virus**
- **Can become latent in infected subjects**
- **Can shed from infected persons**
- **Can infect patient contacts and HCPs**

Goals of the Shedding Study

To determine:

- The mode (route) of shedding**
- The duration (time) of shedding**
- The magnitude (amount) of shedding**

Amgen Shedding Study

(Protocol # 20120324)

Subjects were monitored for the presence of viral DNA at the following sites and body fluids:

- Site of Injection**
- Outside of Occlusion Dressing**
- Blood**
- Urine**
- Oral Mucosal Swab**
- Herpetic Lesions**

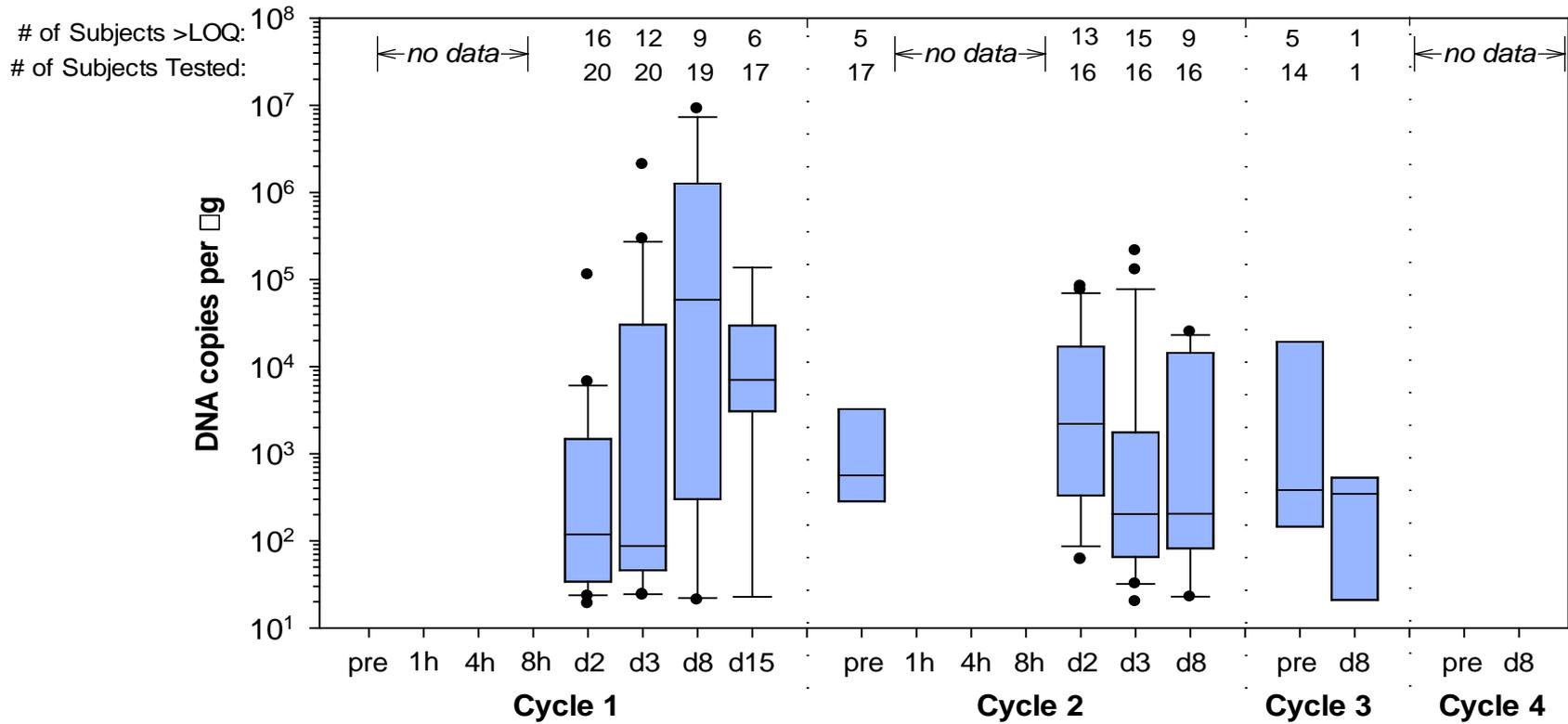
Assays Methods

- **QPCR specific for talimogene laherperepvec DNA was performed on all samples**
- **Assay for Infectious virus performed on QPCR positive samples, except for blood and urine**
- **The QPCR data is expressed as genomic copies/microgram (gc/ug) of host DNA**

Shedding Study Status

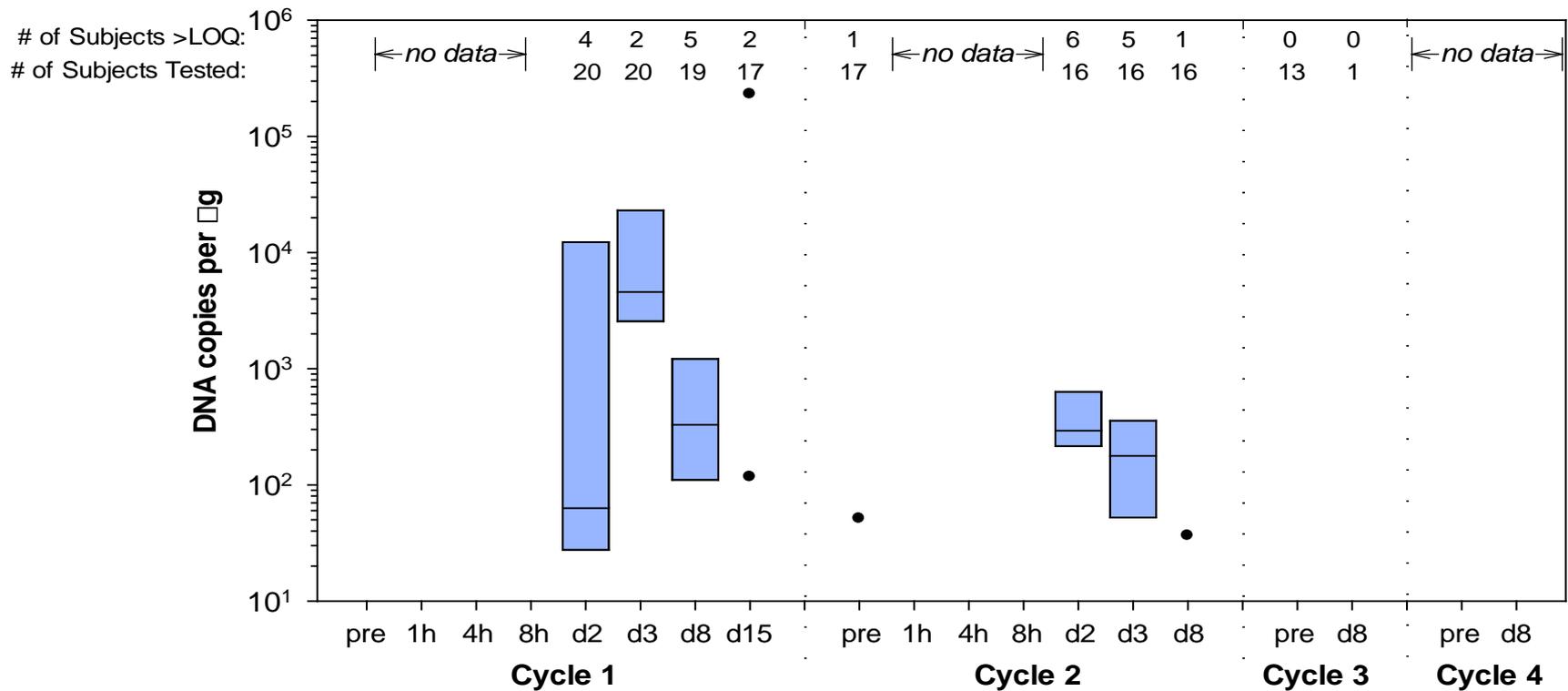
- **25 of the planned 40 subjects treated**
- **Available data from 20 subjects are summarized**
- **Data are incomplete**
- **Data trends reported (FDA's analysis)**

Talimogene Laherparepvec DNA at the Injection-Site



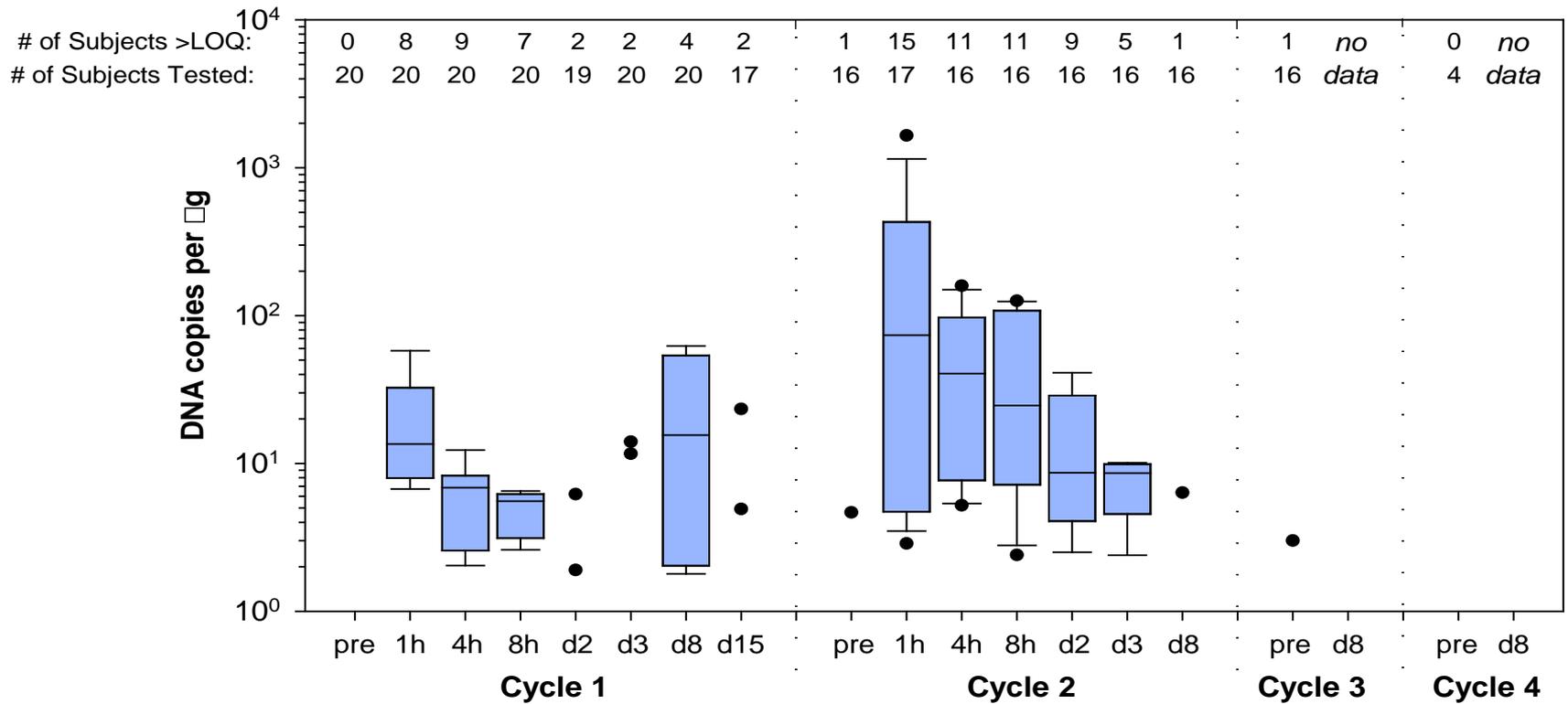
Source: FDA Analysis

Talimogene Laherparepvec DNA on Occlusion Dressing

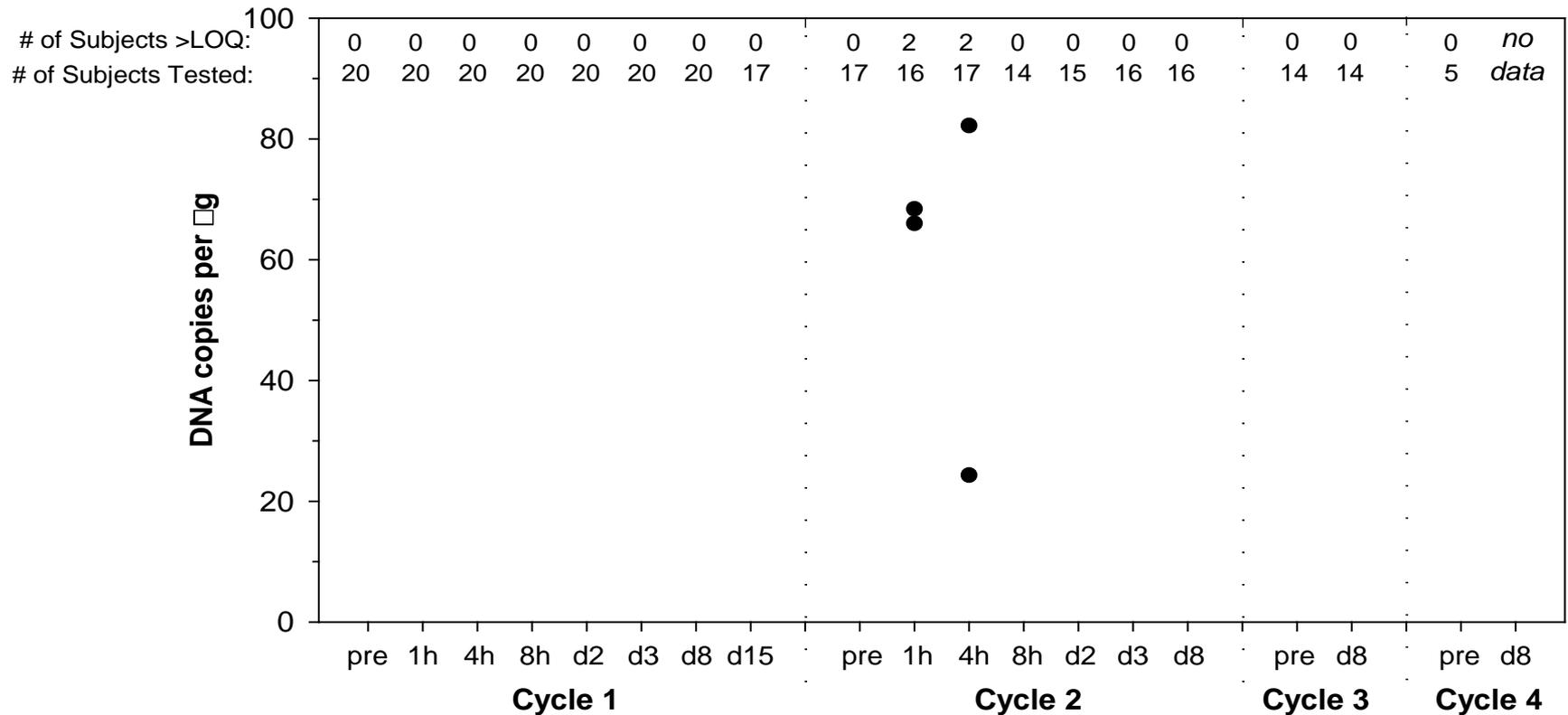


Source: FDA Analysis

Talimogene Laherparepvec DNA in Blood



Talimogene Laherparepvec DNA in Urine



Talimogene Laherparepvec In Oral Mucosa and Herpetic Lesions

Talimogene DNA was not detected in:

- Oral mucosa during the study (4 cycles)
- Herpetic lesions from 7 study subjects
- Lesion positive HCP

Shedding Data Trends (1)

Duration of Shedding:

- Persists at the injection-site
- Passes through the dressing
- May undergo limited in vivo amplification
- Most subjects (>93%) cleared DNA from blood before next injection
- Present in urine on the day of injection

*Due to loss in virus recovery and limitations with methods, the presence of viral DNA may indicate potentially infectious virus

Shedding Data Trends (2)

Magnitude of Shedding:

- No viral DNA was detected in the saliva.
- No viral DNA was detected in tested herpetic lesions in treated subjects or HCP.

Peak viral DNA in:

- Blood: 1650 gc/ug
- Urine: 82.2 gc/ug
- Injected lesions: 9.09×10^6 gc/ug
- Occlusive dressings: 2.3×10^5 gc/ug

Peak titers are from individual samples and do not represent the mean titers

Overall Shedding Summary

Risk for virus transmission is:

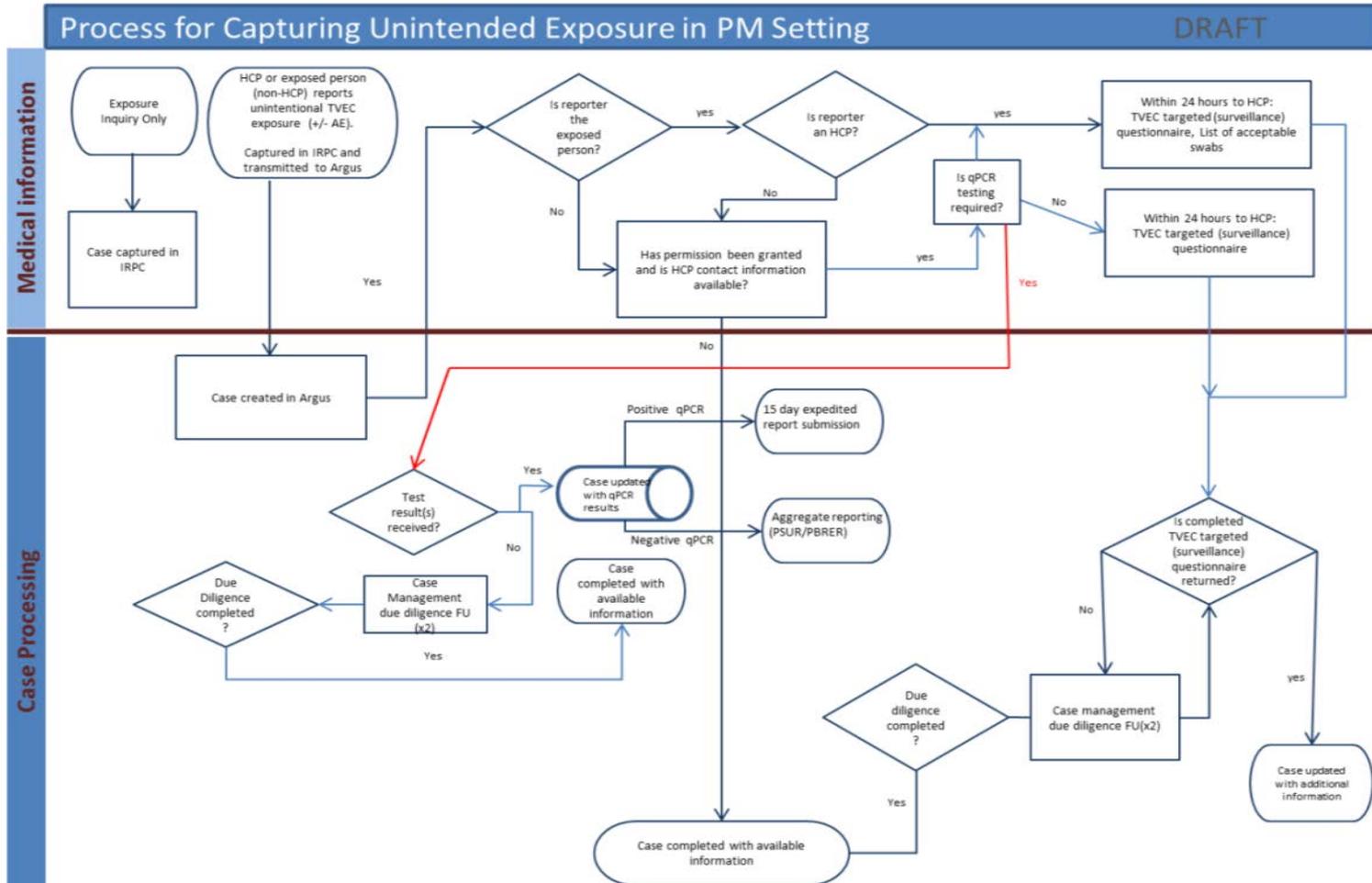
- Greatest due to contact with injection-site or occlusion dressing.
- Blood should be considered potentially infectious.
- Urine may be infectious on the day of injection.

Proposed Postmarketing Assessment of Talimogene Laherparepvec Transmission

- **Study design:**
 - prospective, observational, open-label, single-arm, multi-center cohort study
- **Study duration:**
 - 5 years; goal enrollment: 920 subjects
- **Outcome assessment:**
 - Suspected herpetic infections (in subjects and contacts) will be tested by qPCR for product DNA

Study Design for Assessing Transmission

Figure 1. Process for Capturing Unintended Exposure in PM Setting (Revised)



Concerns with Proposed Study of Talimogene Laherparepvec Transmission

- **Spontaneous reporting by contacts**
- **Multi-step process involves possibly 2 visits to HCP:**
 - initial presentation of lesion
 - swabbing of lesion (after HCP is contacted by Amgen)
- **May be logistically difficult for primary HCP**
 - choose correct swabs
 - ship to testing laboratory
- **Complex, multi-step process**
 - may not be feasible for timely collection of samples from lesions during active infection to achieve results in the real world clinical setting.

Review Issues

Evidence of Effectiveness

- **Appropriateness of GM-CSF as study control**
- **Open-label study led to more early dropouts on the control arm and the length of follow-up was different between the two arms of the study**
- **The EAC did not review data from all subjects in the ITT population potentially leading to assessment bias**
- **The small lesion size potentially influenced the reliability of the outcome assessments**
- **The primary basis for effectiveness comes from a single phase 3 study**

Clinical Benefit

- **Clinical meaningfulness of the novel primary endpoint**
- **Talimogene laherparepvec was given as a local intralesional therapy for melanoma in the setting of a systemic disease**
 - **Limited evidence of systemic effect**
 - **Evidence of responses in uninjected lesions limited and difficult to quantitate**
 - **No immunological response data to correlate with clinical outcome**
- **Unclear whether talimogene laherparepvec administration was associated with improvement in overall survival in the ITT population.**

Safety

- **The most common treatment-emergent adverse events in the talimogene laherparepvec arm were fatigue, chills, pyrexia, nausea, influenza-like illness, and injection-site pain.**
- **Cellulitis at the injection-site and immune-related adverse events were observed.**

Patient Population

- **The appropriate patient population for talimogene laherparepvec given the current melanoma treatment landscape.**
- **Talimogene laherparepvec studied in subjects with unresectable melanoma, but proposed indication omits “unresectable”**

Dosing Regimen

- **Administration was variable, with investigator discretion in the selection of:**
 - **lesions to be injected**
 - **number of lesions to be injected**
 - **dose administered into each lesion**
 - **total dose administered per treatment**
 - **frequency of injections**
- **Difficult to assess the relationship between specific aspects of dosing and the study efficacy results**
- **There may be insufficient information to inform healthcare providers on safe and effective use**

Viral Shedding

Limited data on talimogene laherparepvec shedding to assess risk of viral transmission to healthcare providers (HCPs) and close patient contacts

Voting Question

- **FDA asks the Committee to vote on traditional approval for talimogene laherparepvec based on the BLA submitted**
- **FDA has the regulatory flexibility to consider either traditional approval or Accelerated Approval**
- **FDA could approve the product for either the proposed indicated population, or for a subgroup of the proposed population**
- **FDA will consider all the advice from the committee**

Thank You