WEB ANEURYSM EMBOLIZATION SYSTEM

SPONSOR EXECUTIVE SUMMARY

NEUROLOGICAL DEVICES ADVISORY COMMITTEE

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ADVISORY COMMITTEE BRIEFING MATERIALS: CONFIDENTIAL

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LIST OF ABBREVIATIONS

Abbreviation	Term
ACA	Anterior Cerebral Artery
AComm	Anterior Communicating Artery
AE	Adverse Event
AESI	Adverse Events of Special Interest
CC	Completed Cases
CCT	Cerecyte Coil Trial
CEA	Clinical Events Adjudicator
CI	Confidence Interval
CT	Computed Tomography
DMC	Data Monitoring Committee
EV	Enhanced Visualization
EVT	Endovascular Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IA	Intracranial Aneurysm
ICA	Internal Carotid Artery
ICAt	Internal Carotid Artery terminus
IDE	Investigational Device Exemption
ITT	Intent to Treat
LCL	Lower Confidence Limit
MAR	Missing at Random
MCA	Middle Cerebral Artery
mGy	Milligray
mGy/kg	Milligray per kilogram
MNAR	Missing Not at Random
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
OPC	Objective Performance Criterion
PComm	Posterior Communicating Artery
PG	Performance Goal
PMA	Premarket Approval
PP	Per Protocol
SAE	Serious Adverse Event
SAH	Subarachnoid Hemorrhage
SE	Standard Error
SD	Standard Deviation
TIA	Transient Ischemic Attack
UCL	Upper Confidence Limit
US	United States
WDC	WEB Detachment Controller
WEB	WEB Aneurysm Embolization System
WEB-IT	WEB Intrasaccular Therapy Study
WEB SL EV	WEB Single Layer – Enhanced Visualization
WEB SLS EV	WEB Single Layer Sphere - Enhanced Visualization
WNA	Wide Neck Aneurysm

Abbreviation	Term
WNBA	Wide Neck Bifurcation Aneurysm
WOS	WEB Occlusion Scale

1 SYNOPSIS

1.1 Introduction

The WEB Aneurysm Embolization System (WEB) is a braided implant intended for the treatment of wide neck bifurcation aneurysms (WNBAs). A WNBA is a saccular aneurysm that forms at a bifurcation, or the "Y" segment, of an artery and has a neck size greater than 4 mm or a dome-to-neck ratio less than 2.

The WEB, developed by Sequent Medical[1], consists of an implantable intrasaccular embolization device attached to a delivery system that is navigated through a neurovascular microcatheter to the aneurysm and detached with the WEB Detachment Controller (WDC).

The WEB received CE mark in 2010 and has been approved and commercialized in 44 countries. The WEB has been well studied and used in clinical practice outside of the United States (US) for 8 years. Experience with the WEB includes enrollment of over 260 patients in clinical studies and use in clinical practice with over 6,000 patients treated worldwide.

As demonstrated in the pivotal WEB Intrasaccular Therapy Study (referred to hereafter as WEB-IT), the WEB provided effective treatment of WNBAs with a safety profile that is improved over currently available treatment options based on the following key findings:

- WEB-IT met its primary effectiveness endpoint; 54.8% of patients met the primary composite effectiveness endpoint at 12 months, which was statistically significantly higher than the prespecified Objective Performance Criterion (OPC) of 35% ($p < 0.0001$).
- WEB-IT met its primary safety endpoint with an event rate of 0.67%, which was statistically significantly lower than the prespecified Performance Goal (PG) of 20% ($p < 0.0001$).

1.2 Indications for Use

The original Indications for Use (as presented in the PreMarket Approval application):

> The WEB Aneurysm Embolization System is indicated for the embolization of intracranial wide neck bifurcation aneurysms.
>
> The WEB Aneurysm Embolization System is further indicated to embolize intracranial wide neck bifurcation aneurysms ranging in size from 3 mm to 10 mm in dome diameter, where the neck size is 4 mm or greater or the dome-to-neck ratio is less than 2.

The Sponsor proposes to modify the Indications for Use to better reflect morphology and location of aneurysms tested in the WEB-IT study to the following:

> The WEB Aneurysm Embolization System is indicated for the embolization of intracranial WNBAs.

[1] Sequent Medical, Inc., was acquired by Terumo/MicroVention in July 2016. Sequent Medical, Inc. remains a separate business entity and legal manufacturer, however, some processes and personnel are outsourced and/or shared between Sequent and Terumo/MicroVention.

The WEB Aneurysm Embolization System is further indicated to embolize saccular intracranial WNBAs located in the anterior (middle cerebral artery (MCA) bifurcation, internal carotid artery (ICA) terminus, anterior communicating artery (Acomm) complex) and posterior (basilar apex) circulations, ranging in size from 3 mm to 10 mm in dome diameter, where the neck size is 4 mm or greater or the dome-to-neck ratio is less than 2.

1.3 Background and Unmet Need

Intracranial aneurysms (IAs) are a serious condition associated with a substantial rate of complications leading to morbidity and mortality. The reported prevalence of IAs is between 2-5% of adults (Vlak et al. 2011). Cigarette smoking, hypertension, and family history are risk factors for developing IAs. Approximately 23-36% of all IAs are WNBAs (Naggara et al. 2010, Mitsos et al. 2013, Murayama et al. 2013, Backes et al. 2014, McDougall et al. 2014, Qui and Xing 2014, Bendok 2018, De Leacy et al. 2018, Taschner et al. 2018), which are saccular aneurysms that form at a bifurcation, or the "Y" segment, of arteries and are defined by a neck size greater than 4 mm or a dome-to-neck ratio less than 2.

The greatest risk with any aneurysm is rupture, which may result in subarachnoid hemorrhage (SAH) – a devastating event that is fatal in up to 45% of cases and leaves 40-50% of survivors with major neurologic deficits (Hop et al. 1997, Suarez et al. 2006). Size, location, and previous history may increase the risk of rupture, but the associated severity and catastrophic consequences are independent of size and location of the ruptured aneurysm.

While the treatment of any type of IA can be challenging, WNBAs are a particularly difficult subset of IAs to treat due to their complex anatomy (Fargen et al. 2013). Patients with WNBAs are believed to be at increased risk of sudden and potentially fatal bleeding due to greater arterial flow and pressure into the bifurcation aneurysms compared to typical side-wall aneurysms. The primary goal in treating WNBAs is to prevent ruptures and related morbidity and mortality. The currently available interventions for WNBAs include open surgical clipping and endovascular approaches.

Open surgical clipping is a technique where a clip is placed across the neck of the aneurysm in order to separate it from the vasculature, significantly reducing the risk of rupture. While open surgical clipping appears to demonstrate high immediate occlusion success, it is associated with high morbidity and mortality. Due to a lack of open surgical clipping studies requiring follow-up, long-term occlusion rates cannot be confirmed in the literature. The overall mortality rate reported with surgical clipping is in the range of 2-10% (Lusseveld et al. 2002, Ogilvy and Carter 2003, Vallee et al. 2003, Wiebers et al. 2003, Adeeb et al. 2018), and patients who undergo the surgery experience a permanent morbidity rate of 5-15% (Lusseveld et al. 2002, Ogilvy and Carter 2003). Additionally, not all aneurysms are surgically accessible without introducing additional risk to the patient. In some aneurysm locations, clipping may require brain retraction and could easily result in damage to small branch vessels, called perforator arteries, leading to a devastating stroke outcome.

Current endovascular treatments for IAs are minimally invasive procedures that decrease the morbidity and mortality seen in open surgery but also may decrease procedural occlusion effectiveness relative to clipping (Rodriguez-Hernandez et al. 2013). Currently available

endovascular treatment options such as coiling and stent-assisted coiling were not specifically designed for WBNAs and may be difficult and less effective to use for this condition.

Treatment of wide-neck aneurysms (side-wall and bifurcation) with coiling alone has been reported to result in 1-year complete occlusion rates of 27%, with permanent morbidity and mortality rates of 1.5%. Stent-assisted coiling increases 1-year complete occlusion rates to 46% but also increases morbidity and mortality rates to 7% (Hetts et al. 2014). The recently published BRANCH Study, which focused exclusively on WNBAs, reported 30.6% 1-year complete occlusion rates and 5.8% morbidity and 1.7% mortality rates for coiling alone, balloon-assisted coiling, and stent-assisted coiling combined (De Leacy et al. 2018). Some currently used implantable endovascular devices, such as stents and flow diverters, require patients to be treated with dual antiplatelet therapy, which is a limiting factor for the treatment of ruptured aneurysms.

Finally, clinicians and patients may prefer a more conservative approach of non-invasive medical management alone. These patients undergo regularly scheduled follow-up imaging to assess the aneurysm growth and are advised to reduce risks factors that may contribute to rupture, such as smoking.

In summary, few options are available to safely and effectively treat the specific size, shape, and location of WNBAs. A new approach to treating WNBAs is needed to overcome the challenges of these particularly difficult to treat IAs.

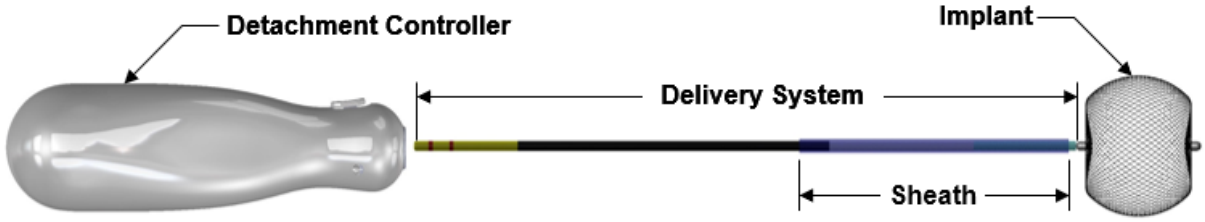
1.4 Product Overview

1.4.1 Device Description

The WEB is a novel, first-of-a-kind device specifically designed for treating WNBAs. The WEB has 3 main components: a braided implant, a delivery system, and the WDC (Figure 1). The WEB implant is available in 2 shapes – barrel and sphere – and a variety of sizes ranging from 4x3 mm to 11x9 mm. The braided composite wires of the WEB are made from Nitinol and platinum and are held together by proximal and distal platinum markers, which facilitate implant delivery under fluoroscopic visualization. The proximal marker recess is a small, conical depression of the device to ensure that the proximal marker of the WEB stays within the aneurysm sac.

Similar to embolization coils, the WEB comes pre-loaded onto a flexible delivery system. The WDC is a hand-held, battery-powered device that enables the physician to electro-thermally detach the implant from the delivery system.

Figure 1: WEB System with WEB Detachment Controller



The braided implant is designed to be placed entirely within the WNBA sac. The proximal marker was specifically constructed to keep all components of the WEB within the aneurysm sac and out of the parent artery. The recessed area of the implant is the most densely braided part of the device, providing up to 100% metal coverage at the neck of the aneurysm. Importantly, with no components of the WEB protruding outside of the aneurysm, and like embolization coils, patients are not required to stay on dual antiplatelet therapy after the implantation procedure.

1.4.2 Implantation Procedure

The WEB is delivered to the treatment site on the delivery system through standard neuro-interventional microcatheters. The initial WEB size is chosen based upon angiographic assessment of the aneurysm dome diameter, dome height, and neck width of the aneurysm to be embolized. The WEB can be repositioned within the aneurysm and if necessary the undetached implant can be retracted into the microcatheter, removed, and exchanged for another WEB device.

1.4.3 Mechanism of Action

While the design of the WEB device is new and unique, the mechanism of action is well known. Similar to coils, upon deployment, the WEB disrupts blood flow into the neck of the aneurysm. Placement of the WEB leads to blood stagnation, clot formation, exclusion of the weakened wall of the aneurysm from circulation, and prevention of aneurysm growth and rupture.

1.5 WEB-IT Study Design

WEB-IT was a prospective, multicenter, single-arm study to evaluate the safety and effectiveness of the WEB in 150 patients with WNBAs. WEB-IT was conducted across 27 centers (21 US centers and 6 international centers).

WEB-IT was a prospective, multicenter, single-arm study to evaluate the safety and effectiveness of the WEB in 150 patients with WNBAs. WEB-IT was conducted across 27 centers (21 US centers and 6 international centers).

WEB-IT was the first prospective clinical study focused specifically on the rate of complete occlusion in WNBAs. Due to the absence of a single standard-of-care treatment option for WNBAs, a single-arm study design was chosen. Using the Agency's suggested methodology, an objective performance criterion (OPC) was calculated to measure effectiveness. This OPC methodology was recently published (Fiorella *et al.* 2017). As advised, a safety performance goal (PG) was chosen in alignment with similar devices.

<u>Effectiveness Objective Performance Criteria (OPC)</u>

The effectiveness OPC was based upon a comprehensive review of published medical literature on the treatment of WNBAs in 2013. The OPC was defined as the lower two-sided 95% confidence limit of the Core Laboratory adjusted point estimate of complete occlusion from the data included in these studies. This original OPC was derived as a success rate statistically greater than 35% for the primary endpoint – the proportion of patients with complete aneurysm occlusion without retreatment, without recurrent SAH, and without clinically significant (> 50%) parent artery stenosis

at 12 months. The Sponsor conducted an additional comprehensive literature review at the time of Premarket Approval (PMA) submission in 2017, which derived an updated OPC of 39%.

A recent peer-reviewed meta-analysis of literature related to the treatment of WNBAs reported a Core Laboratory adjusted OPC of 39.3% (Fiorella et al. 2017). The OPC was based on all types of treatment modalities for wide-neck intracranial aneurysms including endovascular and open surgical treatments and further supported by the independent, physician-led, retrospective, multicenter BRANCH study in 2018, which showed a Core Laboratory adjudicated complete occlusion rate at 12 months of 30.6% with a lower 95% confidence interval (CI) of 22% in 115 patients with unruptured WNBAs treated using currently available treatments (De Leacy et al. 2018).

Safety Performance Goal (PG)

The safety PG was established as a failure rate of less than 20% at 12 months on the primary safety endpoint – the proportion of patients with death of any nonaccidental cause or any major stroke within the first 30 days after treatment or major ipsilateral stroke or death due to neurologic cause from day 31 to 12 months after treatment. A safety PG was originally derived from the rates of primary safety events reported in a meta-analysis of the clinical literature for endovascular and surgical methods of treatment of bifurcation and wide neck IAs. Based on this analysis, the upper two-sided 90% CI was 25.8%. The Agency advised the Sponsor that, for similar devices, a safety PG be defined as the upper limit of the 95% confidence interval being less than 20%. For reference, in approved marketing applications of similar devices (e.g. Pipeline, LVIS, & Surpass), a primary safety PG of 20% was used.

Study Oversight

The Sponsor incorporated several controls to maintain oversight of WEB-IT. An independent Core Laboratory evaluated all angiographic images to ensure that the effectiveness of the device was determined by unbiased assessment of imaging results. All adverse events (AEs), device failures, and site reported deviations were reviewed by an independent Clinical Events Adjudicator (CEA). A Data Monitoring Committee (DMC) provided oversight during the study to ensure patient safety.

Patient Population

To be included in the study, patients had to be between 18 and 75 years of age with a single ruptured or unruptured WNBA. Aneurysms were required to have the following characteristics:

- Saccular in shape
- Located in the basilar apex, middle cerebral artery (MCA) bifurcation, internal carotid artery terminus (ICAt) or anterior communicating artery (AComm) complex
- Dome-to-neck ratio of ≥ 1
- Neck size ≥ 4 mm or dome-to-neck < 2

Inclusion Criteria

Patients could be included in the study only if they met **all** of the following inclusion criteria.

1) Patient must be 18-75 years of age at the time of screening.

2) Patient must have a single ruptured or unruptured IA requiring treatment. If the patient had an additional IA requiring treatment, the additional IA must not require treatment within 60 days of the index procedure.

*Definition: For the purposes of this study a **ruptured IA** patient was defined as a patient with computed tomography (CT), magnetic resonance imaging (MRI), or lumbar puncture (LP) evidence of subarachnoid hemorrhage attributed to the index aneurysm within the last 60 days.*

3) The IA treated must have had the following characteristics:
    a. Saccular in shape
    b. Located in basilar apex (BA), middle cerebral artery (MCA) bifurcation, internal carotid artery terminus (ICAt), anterior communicating artery complex (ACom)
    c. Dome-to-Neck (DN) ratio ≥1
    d. Diameter of the IA appropriate for treatment with the WEB Aneurysm Embolization System per device Instructions for Use
    e. Wide-neck IA with neck size ≥ 4mm or Dome-to-Neck (DN) < 2;
4) Patient had an IA that was appropriate for treatment with WEB without the use of additional implanted devices;
5) If the IA previously ruptured, patient must be neurologically stable with Hunt & Hess Score of I or II.
6) Patient was able to comply with all aspects of the screening, evaluation, treatment, and the post-procedure follow-up schedule.
7) Patient signed and dated an IRB/EC-approved written informed consent prior to initiation of any study procedures.

Exclusion Criteria

Patients were excluded from the study for **any** of the following reasons:

1) Patient had an IA with characteristics unsuitable for endovascular treatment;
2) Microcatheter did not reach patient's index aneurysm to allow necessary access to treat with study device.
3) Patient had vessel characteristics, tortuosity or morphology which precluded safe access and support during treatment with study device;
4) Patient had vascular disease or other vascular anomaly that precluded the necessary access to the aneurysm for use of the study device.
5) Patient had clinical, angiographic or CT evidence of vasospasm, vasculitis, an intracranial tumor (except small meningioma) or any other intracranial vascular malformations on presentation;
6) Patient had conditions placing them at high risk for ischemic stroke or had exhibited ischemic symptoms such as transient ischemic attacks, minor strokes, or stroke-in-evolution within the prior 60 days;

7) Patient had any circulatory, neurovascular, cardiovascular, or neurologic conditions that resulted in unstable neurological symptoms
8) Patient had mRS ≥ 2 prior to presentation or rupture (as applicable);
9) Patient had an SAH from a non-index aneurysm or any other intracranial hemorrhage within 90 days;
10) Patient had physical, neurologic or psychiatric conditions which precluded his/her ability to comply with all aspects of the screening, evaluation, treatment, and the post-procedure follow-up schedule;
11) Patient's index IA was previously treated;
12) Patient was taking anticoagulants or had a known blood dyscrasia, coagulopathy, or hemoglobinopathy;
13) Patient was pregnant;
14) Patient had known hypersensitivity, which could not be medically treated, to any component of the study device, procedural materials, or medications commonly used during the procedure;
15) Patient was concurrently involved in another investigational study or a postmarket study that could affect the safety and effectiveness of IA treatment with the study device or with the study's follow-up schedule;
16) Patient had an acute life-threatening illness other than the neurological disease to be treated in this trial;
17) Patient had a life expectancy of less than 5 years due to other illness or condition (in addition to an intracranial aneurysm).

Study Phases

WEB-IT consisted of 3 phases: Screening, Treatment, and Follow-up. During the Screening Phase, patients were assessed for the inclusion and exclusion criteria, and those who qualified were consented and proceeded to the Treatment Phase. During the Treatment Phase, angiographic assessments were conducted per standard of care to further confirm patient eligibility. Confirmed patients then underwent a standard endovascular procedure to implant the WEB in the WNBA (details on the implantation procedure can be found in Section 3.2.1).

After treatment, patients entered the Follow-up Phase where assessments were conducted at 1 month, 6 months, and 12 months post-treatment; based on standard of care guidelines, angiographic assessments were conducted at 6 months and 12 months. To evaluate the long-term safety and effectiveness of the WEB, all patients who entered into the study were consented to be followed long-term for up to 5 years.

Effectiveness Endpoints

Primary Effectiveness Endpoint

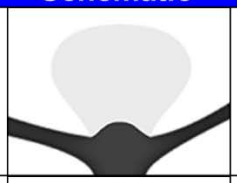
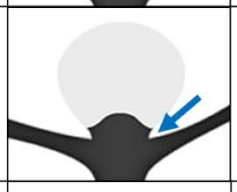
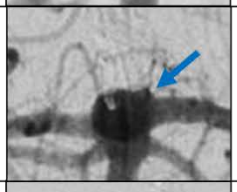
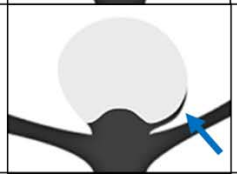
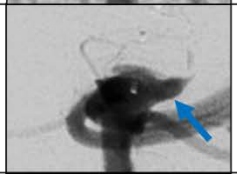
The primary effectiveness endpoint was a composite endpoint of the proportion of patients at 12-months post-treatment with complete aneurysm occlusion on the WEB Occlusion Scale (WOS) without retreatment, without recurrent SAH, and without clinically significant (> 50%) parent artery

stenosis. As mentioned above, the results for the primary effectiveness endpoint, determined by the lower limit of the one-sided 95% CI, were compared to the prespecified OPC of 35%.

Given the novel design of the WEB, the WOS was developed as a modification of the Raymond-Roy Occlusion Classification Scale (Roy et al. 2001). Similar to the Raymond Scale, Complete Occlusion was considered a success, and Neck Remnant and Aneurysm Remnant were considered failures in WEB-IT. The WOS, shown in Figure 2, was validated to assess occlusion in patients receiving the WEB.

As shown in the schematic and angiogram example for Complete Occlusion in Figure 2, the proximal marker recess does not affect complete occlusion of the aneurysm, and no contrast can be seen beyond the recess into the aneurysm. This outcome is easily distinguishable from a Residual Neck or Neck Remnant on angiographic assessment. Complete occlusion in the scale may have two angiographic signatures: 1) Complete Occlusion (not shown) and 2) Complete Occlusion with a marker recess that is more applicable to the WEB design (shown in Figure 2).

Figure 2: The WEB Occlusion Scale

Grade	Definition	Schematic	Angiogram
Complete Occlusion	No contrast in contact with the IA neck or with the wall of the IA sac		
Residual Neck	Some contrast in contact with IA neck but no contrast in contact with wall of the IA sac or the inside of WEB device		
Residual Aneurysm	Apparent contrast in contact with the IA sac or the inside of the WEB device		

Safety Endpoints

The primary safety endpoint was the proportion of patients with death of any nonaccidental cause or any major stroke within the first 30 days after treatment or major ipsilateral stroke or death due to neurologic cause from day 31 to 12 months after treatment. As previously mentioned, the statistical test for the primary safety endpoint was a failure rate of < 20% compared to the one-sided 95% CI.

A Major stroke is defined in the WEB-IT Study Protocol as a stroke resulting in an increase in the NIH Stroke Scale by > 4 at the time of assessment AND which remains present after 7 days),

Patient Disposition

A total of 179 patients were consented for possible participation in WEB-IT, and 150 patients were enrolled and underwent the WEB implantation procedure.

Statistical Analyses

The primary analysis was conducted on the Intent-to-Treat (ITT) Population, which included all 150 enrolled patients who had a WEB implantation attempt. Additional analyses were conducted on the Completed Case (CC) and Per Protocol (PP) Populations, which were identical and included the 143 patients with 12-month evaluations for effectiveness.

For the ITT analysis of the primary safety and effectiveness endpoints, patients with missing data were categorized as either missing at random (MAR) or missing not at random (MNAR). Patients categorized as MNAR were considered failures for the primary effectiveness endpoint. Patients who were absent at 12 months were assumed to be MAR and had their success or failure imputed for the primary safety and effectiveness endpoints. For the imputation, these patients were grouped by aneurysm location, rupture status, size, and 6-month finding if available; imputed patients were assigned the occlusion status and parent vessel score of a similar patient. Imputation was performed 20 times each with a randomly chosen 5-digit seed used for generation of random numbers. These imputations were included in the primary effectiveness and safety endpoint results.

1.6 Effectiveness Results

Demographics and Baseline Characteristics

Baseline demographics in WEB-IT were representative of the patient population with IAs. The average age of patients enrolled in WEB-IT was 59 years old, 73% were female, and 85% were White (Table 1). Approximately 44% of patients were current smokers, and an additional 21% had smoked in the past.

Table 1: Patient Baseline Demographics in WEB-IT

Variable	ITT Population N=150
Age (years), mean (SD)	58.98 (10.16)
Female, n (%)	110 (73.33%)
Race, n (%)	
White	98 (84.48%)
Black or African American	14 (12.07%)
Other	4 (3.45%)
Smoking status, n (%)	
Current smoker	66 (44.00%)
Past smoker	32 (21.33%)

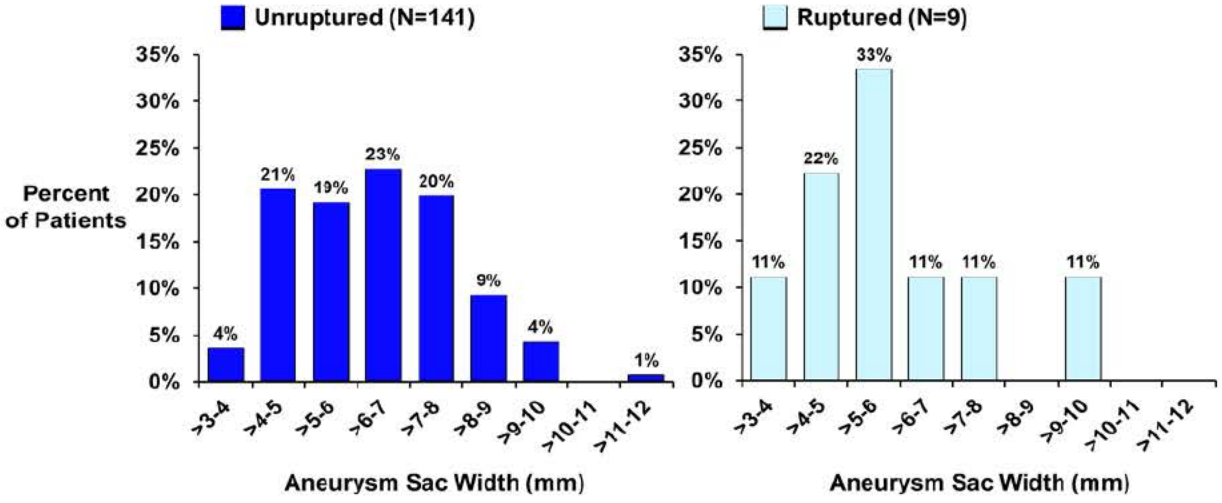
Baseline aneurysm characteristics are shown in Table 2. Mean aneurysm sac width was 6.4 mm with a mean neck width of 4.8 mm. The majority of patients enrolled in the study had unruptured aneurysms. The WEB demonstrated an ability to treat most WNBAs regardless of rupture status, and patients presenting with unruptured and ruptured aneurysms were included in WEB-IT and the primary analyses. The distribution of aneurysm locations in the study population mainly reflects the distribution of aneurysm locations in the general population of patients treated with IAs.

Table 2: Aneurysm Baseline Characteristics in WEB-IT

Variable	ITT Population N=150
Sac width (mm), mean (SD)	6.4 (1.6)
Neck width (mm), mean (SD)	4.8 (1.1)
Rupture status, n (%)	
Ruptured	9 (6.00%)
Unruptured	141 (94.00%)
Aneurysm Location, n (%)	
AComm	40 (26.67%)
Basilar	59 (39.33%)
ICA	6 (4.00%)
MCA	45 (30.00%)

The distribution of aneurysm sizes in WEB-IT ranged from >3 to <12 mm (Figure 3).

Figure 3: Baseline Aneurysm Size by Rupture Status in WEB-IT



Procedural Characteristics

The mean procedure time for WEB implantation was approximately 21 minutes, with less than 31 minutes of total fluoroscopy time and a total fluoroscopy dose of 2,756 mGy (Table 3). It is important to note that additional imaging was required by protocol in WEB-IT, so fluoroscopy would likely be reduced in a clinical use setting.

Table 3: WEB Implantation Procedure Information in WEB-IT

Variable	Mean (SD)
Total WEB procedure time (min)	20.9 (21.2)
Fluoroscopy time (min)	30.2 (15.7)
Total Fluoroscopy Dose (mGy)	2756 (2582.4)

A total of 211 WEB devices were used in WEB-IT, resulting in 148 successfully implanted (Table 4). As discussed in Section 1.4, the physician can review and adjust the device fit within the

aneurysm after deployment but prior to detachment from the WEB delivery system. Of the 63 WEB devices that were attempted but not implanted, 89% were replaced by the investigator to optimize device fit. The majority of patients (67%) had a WEB implanted in 1 attempt, and 26.67% required 1 resizing to ensure proper fit and resulted in successful implantation of a WEB.

Table 4: WEB Selection and Implantation Characteristics

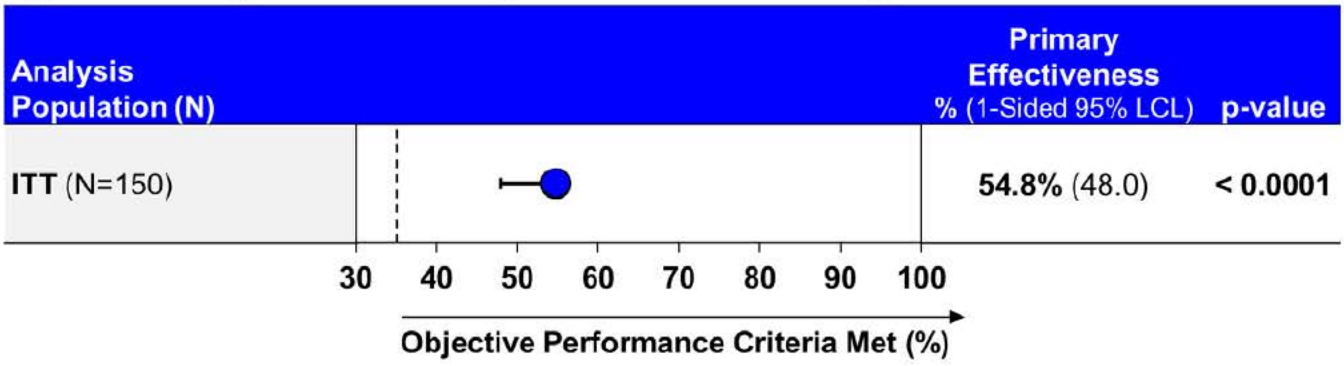
	WEB Devices	
	N	%
Total WEBs Inserted	211	100%
Total WEBs Implanted	148	70%
Not Implanted	63	30%
Number of Attempts (n=150)		
1	100	66.67%
2	40	26.67%
3	9	6.00%
4	1	0.67%

Importantly, regardless of the number of devices attempted prior to final implantation, the ability to safely remove and replace the WEB is supported by the high technical success rate observed in WEB-IT. Overall, 98.7% of patients had a WEB successfully implanted. An adjunctive device was used during the procedure in 7 patients. Adjunctive balloons, which were allowed by the study protocol, were used in 5 cases to assist in positioning of the WEB device, and 2 patients required a stent to ensure the regional branch vessels remained open. The use of stents was not permitted by the protocol and was included in the primary effectiveness analysis as a failure.

Primary Effectiveness Endpoint Results

WEB-IT met the primary effectiveness endpoint with 54.8% of patients at 12 months post-treatment achieving complete aneurysm occlusion without retreatment, without recurrent SAH, and without clinically significant (> 50%) parent artery stenosis (Figure 4). These results were statistically significant ($p < 0.0001$) when compared to the OPC of 35%.

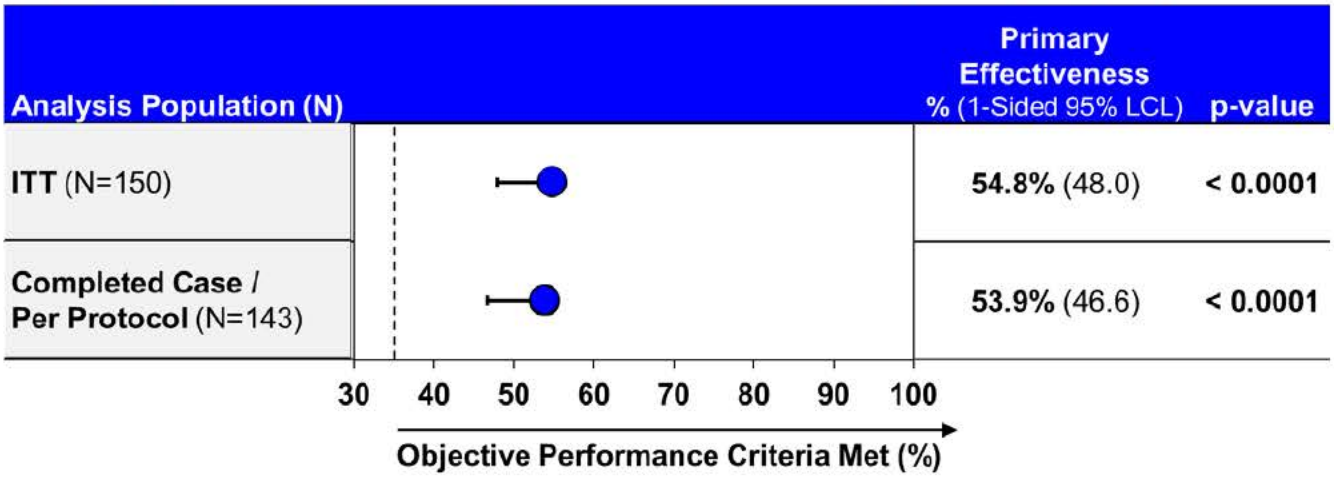
Figure 4: Primary Effectiveness Endpoint Results in the ITT Population in WEB-IT



To assess the effects of the imputation methods used for missing data, the CC/PP Population was also analyzed for the primary effectiveness endpoint results. In the CC/PP Population, which excludes patients who did not have 12 months of data available, 53.9% of patients met the primary

effectiveness endpoint (Figure 5). A tipping point analysis that included all possible imputations including a worst case in which all patients with missing data were failures was also conducted and showed results consistent with the primary effectiveness endpoint analysis.

Figure 5: Primary Effectiveness Endpoint Results in the CC/PP Population in WEB-IT



Breaking down the primary effectiveness endpoint by components (Table 5), 59 of the 66 patients in the CC/PP Population did not meet the primary effectiveness endpoint criteria due to Residual Neck (44 patients [30.8%]) or Residual Aneurysm (15 patients [10.5%]).

Table 5: Patients Not Meeting Primary Effectiveness Endpoint in CC/PP Population in WEB-IT (n=143)

	Patients	
	%	N
Total Not Meeting Primary Effectiveness Outcome	**46.2%**	**66**
Residual Neck	30.8%	44
Residual Aneurysm	10.5%	15
Retreatment within 12 months	2.1%	3
Failure to implant	1.4%	2
Adjunctive device use	1.4%	2

Note: For 1 patient, the primary reason for effectiveness failure was Residual Aneurysm at 6 months, retreated with a stent, with subsequent significant parent artery stenosis at 12 months.
Note: Eight patients required retreatment: 5 patients with retreatment were counted based on the pre-retreatment angiogram and 3 patients without a useable 12-month angiogram were counted in the retreatment category.

An additional analysis (not included in the calculation of primary effectiveness endpoint of adequate occlusion), defined as the proportion of patients achieving Complete Occlusion or Neck Remnant, showed that 83.2% of patients in the CC/PP Population achieved adequate occlusion at 12 months.

1.7 Safety Results

WEB-IT met the primary safety endpoint – the proportion of patients with death of any nonaccidental cause or any major stroke (A stroke, which increases the NIH Stroke Scale by > 4 at the time of assessment AND which remains present after 7 days

) within the first 30 days after treatment or major ipsilateral stroke or death due to neurologic cause from day 31 to the 12 months after treatment – with 1 patient experiencing a primary safety event in 12 months. The observed rate in the ITT Population was 0.67% with upper one-sided 95% limit of 6.04%, which is well below the prespecified PG of 20%. There were no deaths through 12 months and no major ipsilateral strokes reported between days 31 and 12 months.

The single primary endpoint event was a SAH adjudicated as a major stroke, occurring 22 days following WEB implantation. The event was characterized as probably related to the index procedure and/or a concurrent condition or treatment. A full narrative for this patient can be found in Section 6.2.

A summary of all AEs occurring in WEB-IT is shown in Table 6.

Within the first 30 days of implantation with the WEB, 45% of patients experienced 1 or more non-serious AEs. The most commonly reported non-serious AEs during the first 30 days were headache (13%), nausea (6%), and adverse drug reactions (5%).

Similarly, between day 31 and 12 months, 43% percent of patients reported non-serious AEs and 14% experienced SAEs. The most commonly reported non-serious AEs between day 31 and 12 months were headache (13%) and adverse drug reaction (5%). Overall, non-serious AEs reported during the study were infrequent, and nearly all resolved without clinical sequelae.

Table 6: Summary of Adverse Events in WEB-IT

	Events	Patients N=150	
		n	%
Within 30 days			
Any non-serious AE	135	68	45.3%
Any SAE	27	21	14.0%
Day 31 to 12 Months			
Any non-serious AE	151	65	43.3%
Any SAE	35	21	14.0%

Within the first 30 days, 14% of patients experienced SAEs. As shown in Table 7, within the first 30 days, 7% of patients experienced procedure-related SAEs, 1% of patients experienced device-related SAEs, and 2% of patients experienced SAEs that were related to both the procedure and device. Additionally, 6% of patients experienced SAEs within the first 30 days that were not related to the procedure or device; these events included seizure, headache, syncope, and chest pain (1 patient each). Importantly, there were no SAEs considered to be related to the device or the procedure between day 31 and 12 months.

Table 7: Serious Adverse Events Occurring Within 30 Days in WEB-IT

Within 30 Days	Events	Patients N=150	
		n*	%
Any SAE	**27**	**21**	**14.0%**
Procedure-related	11	10	6.7%
Device-related	1	1	0.7%
Procedure & device-related	3	3	2.0%
Not related	12	9	6.0%

*Patients could have more than 1 event in a given category.

Of the 11 procedure-related SAEs (Table 8), the most commonly reported were ischemic stroke (3 patients) and vessel puncture site hematomas (3 patients). There was 1 device-related SAE of SAH that occurred within the first 30 days and was considered to be definitely related to the WEB and probably to an ancillary device, the microcatheter. There were 3 procedure- and device-related SAEs that occurred within the first 30 days: ischemic stroke, transient ischemic attack, and arterial thrombosis.

Table 8: Procedure- and Device-Related Serious Adverse Events Occurring within 30 Days in WEB-IT

Within 30 Days	Events	Patients N=150	
		n	%
Procedure-related SAE	**11**	**10**	**6.7%**
Vessel puncture site hematoma	3	3	2.0%
Ischemic Stroke	3	3	2.0%
Aphasia	1	1	0.67%
Confusional state	1	1	0.67%
Subarachnoid hemorrhage	1	1	0.67%
Transient ischemic attack	1	1	0.67%
Vomiting	1	1	0.67%
Device-related SAE	**1**	**1**	**0.67%**
Subarachnoid hemorrhage	1	1	0.67%
Procedure- and device-related SAE	**3**	**3**	**2.0%**
Ischemic Stroke	1	1	0.67%
Transient ischemic attack	1	1	0.67%
Arterial thrombosis	1	1	0.67%

All strokes were assessed as AEs of special interest (AESIs) in WEB-IT (Table 8). A total of 11 ischemic stroke events occurred in 10 patients. These events included 10 minor ischemic strokes and 1 transient post-procedural aphasia conservatively counted as an ischemic stroke. Of these events, 8 resolved without sequelae and 3 resulted in minor sequelae with mRS scores of 1 at 12 months.

There were 4 hemorrhagic stroke events: 1 SAH (the primary safety event), 2 procedural SAHs, and 1 intracranial hemorrhage. The latter 3 events resolved without sequelae.

Details for these events can be found in Table 33.

Table 9: Adverse Events of Special Interest – All Strokes – in WEB-IT

	Events	Patients N=150	
		n	%
Ischemic Stroke	11	10	6.7%
Hemorrhagic Stroke	4	4	2.7%

1.8 Benefit-Risk Conclusions

WNBAs are an especially difficult subset of IAs to treat due to their location, direct arterial flow and pressure, and incorporation of small branch vessels. Currently available treatment options are limited, and complications from surgical or endovascular treatment of WNBAs are common. Treatment of WNBAs remains an important unmet medical need, with no device currently available that was specifically designed to address the unique challenges presented by ruptured or unruptured WNBAs.

The WEB is an intrasaccular braided device intended for use in endovascular embolization of WNBAs. The intended therapeutic effect of the WEB is to cover the neck of the aneurysm with a metallic structure that disrupts the inflow of blood, causing hemostasis within the aneurysm sac, and leading to thrombus formation within the implant. The design of the WEB overcomes anatomical challenges associated with WNBAs and can be used to treat both ruptured and unruptured aneurysms.

The pivotal study, WEB-IT, was successful as both the primary effectiveness and primary safety endpoints met their respective OPC and PG by a wide margin. Secondary and additional safety and effectiveness outcomes demonstrated similar positive findings for this difficult to treat patient population. An analysis of AE rates further supports an acceptable safety profile for the WEB. These data and analyses provide valid scientific evidence of the safety and effectiveness of the WEB for the treatment of WNBAs.

Data from WEB-IT are also supported by the outcomes of 3 completed single-arm, prospective, post-market, multicenter, studies conducted in compliance with Good Clinical Practice (GCP) guidelines in patients with WNBAs in Europe: WEBCAST (N=51), WEBCAST 2 (N=62), and French Observatory (N=55). A fourth study, CLARYS (N=60), has completed procedures and 30-day follow-up (The CLARYS study results were not presented to the Agency in the PreMarket Approval application). The completed studies showed complete occlusion rates of 52-62% at 12 months, with no mortality and low morbidity related to treatment at 30 days.

Overall, the WEB represents the next generation of cerebral aneurysm implant, providing a minimally-invasive option for treating patients with WNBAs with a positive benefit-risk profile.

2 BACKGROUND ON WIDE-NECK BIFURCATION ANEURYSMS

Summary

- Intracranial aneurysms are a common and potentially lethal disease of the blood vessels, affecting 2-5% of the adult population worldwide.
- Approximately 23-36% of IAs are WNBAs, which are particularly difficult to treat.
- Rupture of an IA results in a SAH, which can be fatal or severely debilitating; therefore, the goal of treatment of any aneurysm is to prevent ruptures and related morbidity and mortality.
- Current treatment options for WNBAs include open surgical clipping and endovascular techniques such as coiling and stent-assisted coiling, but these are limited and carry greater risks for WNBAs compared to other IAs.
- The complex anatomy of WNBAs leads to increased risks, including death and stroke, in both surgical and endovascular procedures.
- Patients would benefit from a new, minimally-invasive option to treat WNBAs that can overcome the challenges of treating these particular IAs.

2.1 Overview of Intracranial Aneurysms

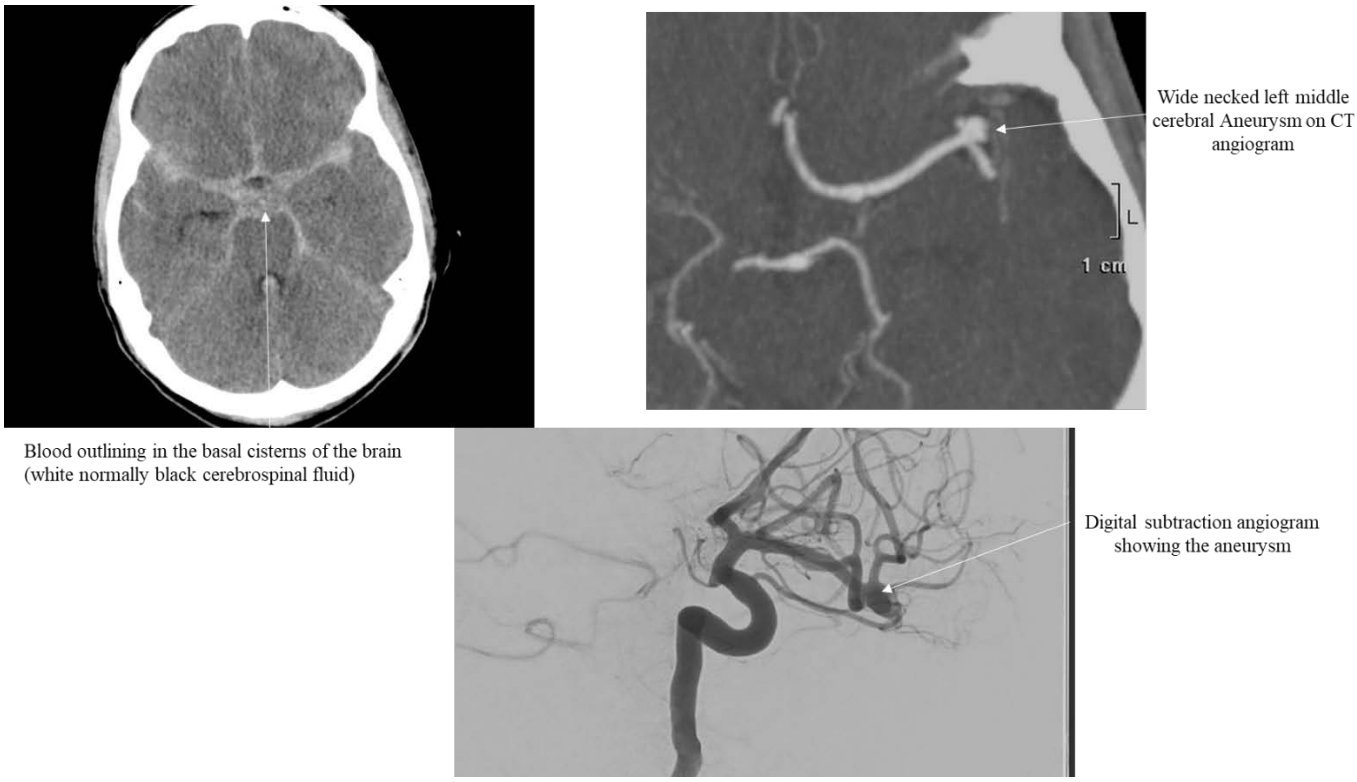
Intracranial aneurysms are a common and potentially lethal disease of the blood vessels affecting 2-5% of the adult population worldwide (Vlak et al. 2011). Intracranial aneurysms occur due to a weakened area of a cerebral artery that causes abnormal dilation of the vessel, forming a sac. The typical age of individuals affected by IAs is 40-60 years old, and IAs are significantly more common in females than in males. Cigarette smoking, hypertension, and family history of IAs are also risk factors for IAs (Rinkel et al. 1998). Additionally, approximately 20% of patients with an IA will have multiple IAs.

The most significant complication of an IA is rupture, which results in a SAH, a devastating event that is fatal in up to 45% of cases and leaves 40-50% of survivors with major neurologic deficits (Hop et al. 1997, Suarez et al. 2006). Approximately 12% of patients with SAH die suddenly, before receiving medical care; rupture of posterior circulation IAs is associated with an even higher sudden death rate of 45% (Huang and van Gelder 2002). Figure 6 shows images of SAHs from ruptured wide-neck IAs.

When an IA ruptures, patients may experience the worst headache of their life, often described as "being hit on the head with a baseball bat." Patients often collapse and may become unconscious. The intracranial pressure rises and causes tamponade of the bleeding aneurysm, and a clot is formed to stop the bleeding. If the bleeding does not stop, some patients will die within minutes of severely raised pressure in the head causing cardiopulmonary shock.

In patients who survive long enough to receive treatment, the bleed will have been stopped by the formation of a clot at the site of the rupture. These aneurysms are at a high risk of re-bleeding, and the priority is to secure the aneurysm as promptly as possible to prevent re-rupture.

Figure 6: Acute Subarachnoid Hemorrhage from Wide-Neck Middle Intracranial Aneurysm (Example not related to WEB-IT study)

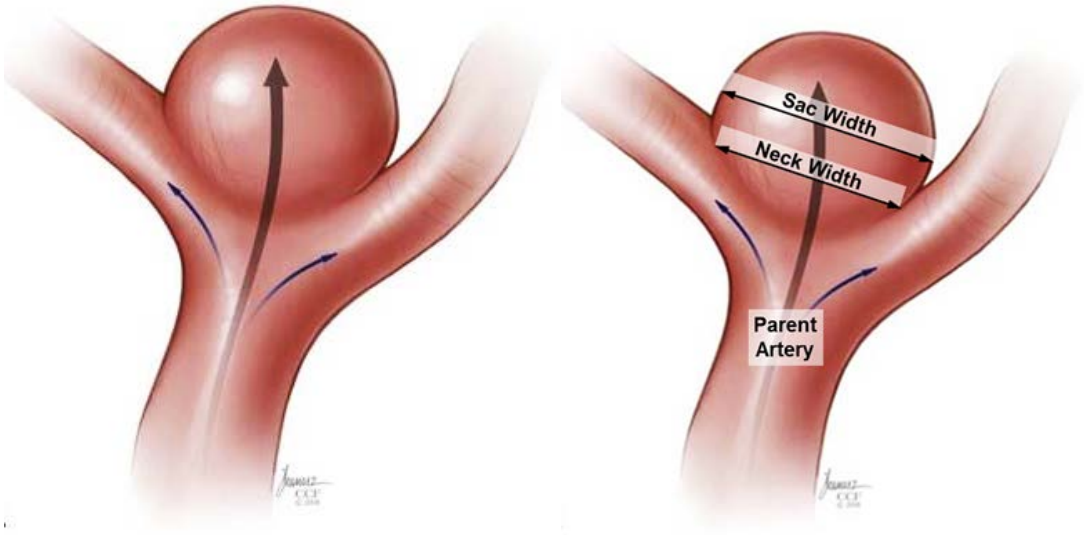


2.2 Wide-Neck Bifurcation Aneurysms

A WNBA is an aneurysm that forms at a bifurcation, or the "Y" segment, of an artery (Figure 7). The neck, or the base, of a WNBA, is at least 4 mm wide, or at least half as wide as the distance from the opening to the top of the aneurysm. Wide neck bifurcation aneurysms represent approximately 23-36% of all IAs (Naggara et al. 2010, Mitsos et al. 2013, Murayama et al. 2013, Backes et al. 2014, McDougall et al. 2014, Qui and Xing 2014, Bendok 2018, De Leacy et al. 2018, Taschner et al. 2018) and have been shown to have higher risk of rupture than side wall aneurysms (Brisman et al. 2006).

Due to their complex anatomy, WNBAs are especially difficult to treat (Fargen et al. 2013). There is often greater arterial flow and pressure into bifurcation IAs than typical side-wall IAs, and the incorporation of small branch vessels (perforators) located either close to the IA neck or arising from the IA sac itself present an additional challenge for treatment.

Figure 7: Wide Neck Bifurcation Aneurysm



2.3 Current Treatment Options for Wide-Neck Bifurcation Aneurysms

The primary goal in treating WNBAs is to prevent ruptures and related morbidity and mortality. Current treatment options include monitoring, open surgical clipping, and endovascular treatment with embolic coils or stent-assisted coils. However, due to their complex anatomy, neurosurgery and existing endovascular treatment options are limited and carry risk (Chalouhi et al. 2012, Fargen et al. 2013).

The most conservative treatment option for WNBAs is medical management, or monitoring. This option involves regularly scheduled follow-up imaging to assess the aneurysm growth and/or any morphological changes. Patients are advised to reduce risks factors that may contribute to rupture, such as elevated blood pressure and smoking. The benefit of this approach is that patients do not undergo any type of surgical procedure which may carry surgical risks; however, this approach does not prevent aneurysm growth or rupture.

Open surgical clipping is another option for treatment of WBNA. However, WNBAs may be difficult to treat with clipping due to the presence of small perforator arteries that can arise from the aneurysm sac itself and must be dissected away from the aneurysm neck; clipping of a WNBA can damage a perforator artery, leading to a devastating stroke outcome (Fargen et al. 2013). Additionally, although clipping may be effective, not all aneurysms can be safely clipped, and the invasive procedure may be associated with high morbidity and mortality. Rodriguez-Hernandez et al. (2013) reported a 9.9% rate of permanent morbidity and mortality with open surgical clipping. Long-term effectiveness of open surgical clipping of WBNA has not been researched.

Similar to the WEB, embolic coils can be inserted through endovascular techniques into an aneurysm to prevent blood from flowing in the aneurysm sac and allow re-endothelialization of the aneurysm neck, shielding the aneurysm sac from arterial pressure and reducing the risk of subsequent rupture. However, coils may not be a suitable option for treatment of WNBAs due to the potential for prolapse of the coil into the parent artery at an arterial bifurcation, which carries a high

risk of acute ischemic stroke. Additionally, the likelihood of complete, stable occlusion with this approach is lower in WNBAs than with narrow-necked aneurysms.

Endovascular stents can be used in combination with coils to treat bifurcation aneurysms (Birknes et al. 2006, Andaluz and Zuccarello 2008, Gao et al. 2013, Bartolini et al. 2014, Guo et al. 2014, Ko et al. 2015, Lee et al. 2016, Limbucci et al. 2016, Castano et al. 2017). However, these techniques demonstrate a higher rate of complications and lower rates of effectiveness in WBNAs and require continued use of dual antiplatelet therapy that carries additional risks, especially for patients with ruptured aneurysms. Stent-assisted coiling is also difficult in WNBAs due to their anatomy, often resulting in the need to deploy stents in complex configurations (Y-stent technique, X-stent technique, waffle cone technique).

Table 10 summarizes the complete occlusion rate and morbidity and mortality associated with coiling and stent-assisted coiling from Hetts et al. (2014). It is important to note that these data are from a mixed population of patients with WNBAs as well as wide-neck sidewall aneurysms, which typically have higher occlusion rates than WNBAs. Although stent-assisted coiling has a higher complete occlusion rate than coiling alone, it also has an increased risk of morbidity and mortality.

Table 10: Current Endovascular Treatment Options

Treatment	Study	Complete Occlusion	Morbidity and Mortality
Coiling	MAPS/Hetts – AJNR 2014 (WNA)	27.1% (12m)	1.5% (12 m)
Stent-assisted coiling	MAPS/Hetts – AJNR 2014 (WNA)	45.7% (12m)	7.5% (12 m)

WNA - wide neck aneurysm cohort - includes sidewall as well as bifurcation aneurysms
Source: Hetts et al. Am J Neuroradiol 2014

Currently available flow diverters (eg, Pipeline Embolization Device) are not designed or specifically indicated to treat WNBAs, and they are contraindicated for patients in whom dual antiplatelet therapy is contraindicated (Pipeline Embolization Device Instructions for Use 2011).

Overall, treatment options for WNBAs are limited and can carry excessive risk. The risks for the composite outcome of stroke/neurologic death have been found to be as high as 10% for endovascular treatment (Birknes et al. 2006) and up to 15% for surgical treatment (Ogilvy and Carter 2003, Sekhar et al. 2007, Chalouhi et al. 2012). Death rates in the range of 2-10% are reported (Lusseveld et al. 2002, Ogilvy and Carter 2003, Vallee et al. 2003, Wiebers et al. 2003), and permanent neurologic morbidity has been found to be in the range of 5-15% (Lusseveld et al. 2002, Ogilvy and Carter 2003).

2.4 Patient Medical Need

Patients with WNBAs would benefit from a new, minimally-invasive approach to treat WNBAs that can overcome the challenges of treating these particular IAs.

3 PRODUCT DESCRIPTION

Summary

- The WEB is an intrasaccular device intended for use in endovascular embolization of WNBAs.
- The WEB System consists of a family of intrasaccular, self-expanding embolization implants attached to a flexible guidewire-like delivery system.
- The WEB is a braided implant composed of Nitinol wires with platinum cores, and platinum radiopaque markers, available in sizes ranging from 4x3 mm to 11x9 mm.
- The WEB is delivered into the IA using standard endovascular neurosurgical embolization techniques and, similar to coils, can be repositioned or removed for a different size prior to detachment by the physician.
- The thrombus-filled WEB creates a mechanical obstruction that prevents blood from flowing into the aneurysm, thereby excluding the weakened aneurysm wall from the circulation.

3.1 Proposed Indication

The original Indications for Use (as presented in the PreMarket Approval application)

> The WEB Aneurysm Embolization System is indicated for the embolization of intracranial wide neck bifurcation aneurysms.
>
> The WEB Aneurysm Embolization System is further indicated to embolize intracranial wide neck bifurcation aneurysms ranging in size from 3 mm to 10 mm in dome diameter, where the neck size is 4 mm or greater or the dome-to-neck ratio is less than 2.

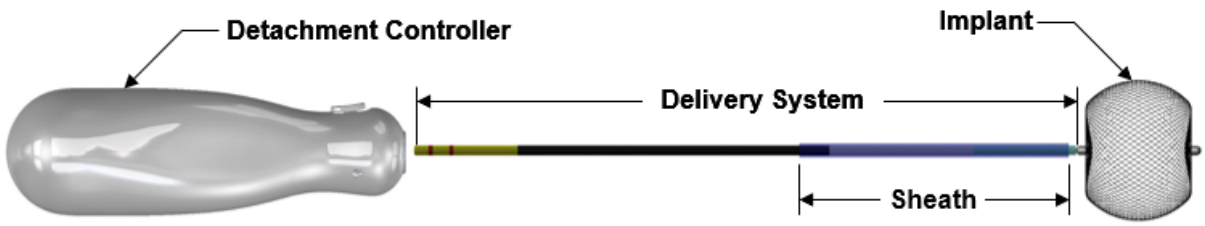
The Sponsor proposes to modify the Indications for Use to better reflect morphology and location of aneurysms tested in the WEB-IT study to the following:

> The WEB Aneurysm Embolization System is indicated for the embolization of intracranial WNBAs.
>
> The WEB Aneurysm Embolization System is further indicated to embolize saccular intracranial WNBAs located in the anterior (middle cerebral artery (MCA) bifurcation, internal carotid artery (ICA) terminus, anterior communicating artery (Acomm) complex) and posterior (basilar apex) circulations, ranging in size from 3 mm to 10 mm in dome diameter, where the neck size is 4 mm or greater or the dome-to-neck ratio is less than 2.

3.2 Device Overview

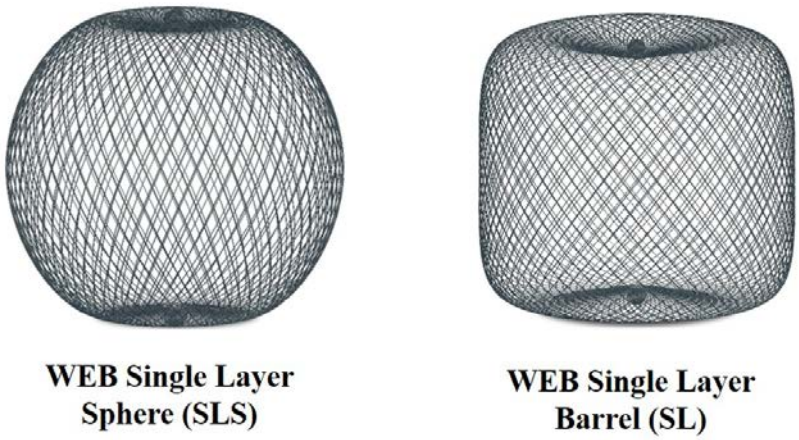
The WEB is a novel, first-of-a-kind device for treating WNBAs. The WEB System consists of a family of intrasaccular, self-expanding embolization implants attached to a delivery system (Figure 8).

Figure 8: WEB System with WEB Detachment Controller



The WEB is a permanent, braided implant composed of single layers of Nitinol wires with platinum cores (Figure 9). The WEB braid is closed at each end by proximal and distal platinum radiopaque markers. The device is available in sizes ranging from 4x3 mm to 11x9 mm and in both barrel and sphere shapes to accommodate the variety of aneurysm sizes and shapes (Figure 9; see Appendix 11.1 for a complete list of available sizes). The barrel shape is recommended for aneurysms with a dome-to-neck ratio of 1:1 to 1.5:1, and the sphere is recommended for dome-to-neck ratios of 1.5:1 to < 2:1.

Figure 9: WEB Implant Shapes: Single Layer Sphere (SLS) and Single Layer Barrel (SL)

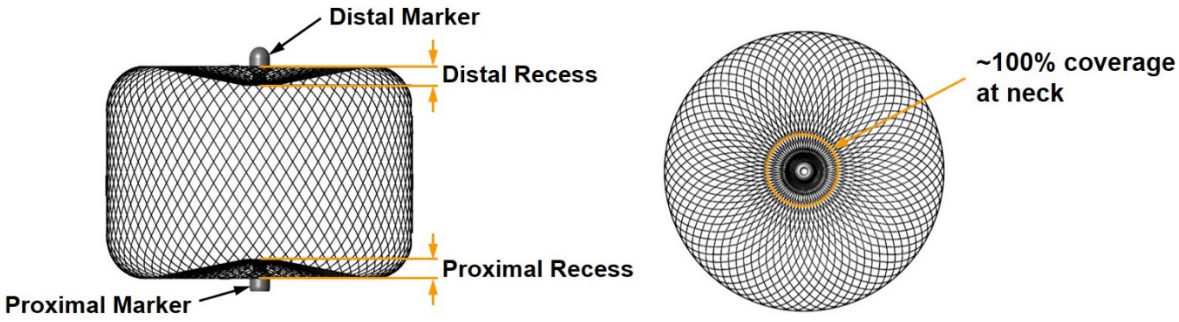


The WEB implants were developed utilizing a composite Nitinol/platinum wire. This filament wire consists of a platinum core surrounded by a Nitinol wire. The Nitinol outer wire provides superelastic properties, and the inner platinum core contributes improved fluoroscopic visibility. All materials used in the WEB implant are commonly used in neurovascular applications. The WEB device is MR Conditional.

The proximal and distal platinum radiopaque markers, shown in Figure 10, facilitate implant delivery under fluoroscopic visualization. Proximal and distal marker recesses are present in all WEB models. The proximal end of all WEB implants incorporates a platinum coupler for attachment to the delivery system. There is approximately zero interwire distance at the proximal marker band/coupler where all the wires converge (approximately 100% metal coverage and approximately zero porosity). The WEB therefore provides high metal coverage where the blood flow attempts to enter the WNBA, providing an intra-procedural flow disruption. The proximal

marker recess was specifically designed to keep the device within the aneurysm sac and the proximal marker out of the parent artery.

Figure 10: Proximal and Distal Marker Recesses



The WEB comes pre-loaded onto the delivery system. The delivery device is connected to a hand-held, battery-powered detachment control device, the WDC, which was designed specifically for the WEB. Detachment of the WEB is accomplished by the WDC via electro-thermal severance of a polymer filament similar to several other commercially-available neurovascular implant delivery systems, including embolization coils.

3.2.1 WEB Implantation Procedure

The WEB device is delivered to the treatment site on the delivery device through standard neuro-interventional wire-reinforced microcatheters with a specified minimum inner diameter using standard endovascular neurosurgical embolization techniques. An introducer sheath on the outside of the delivery device assists in the placement of the system into the microcatheter.

The initial WEB size is chosen based upon angiographic assessment of the dome diameter, dome height, and neck width of the aneurysm to be embolized. Angiographic assessment is again performed after deployment but prior to detachment to ensure that the WEB device is properly deployed within the aneurysm. Like neurovascular embolization coils, the WEB device can be repositioned within the aneurysm or removed after full deployment prior to detachment. If the WEB device fit does not appear ideal within the aneurysm, the device may be retracted into the microcatheter, removed, and exchanged for another WEB device.

After the final WEB position within the WNBA has been confirmed via digital subtraction angiography, the implant is detached from the delivery system with the WDC.

3.3 Mechanism of Action

Although the design of the WEB is unique, its mechanism of action is well known and similar to coiling. Upon deployment into an aneurysm, the WEB expands to contact the lateral walls and cover the aneurysm neck, leading to blood stagnation and promoting formation of thrombus within the aneurysm and device. The resulting thrombus-filled device creates a mechanical obstruction to keep blood from flowing into the aneurysm, thereby excluding the diseased aneurysm wall from the circulation to prevent aneurysm growth and rupture.

4 WEB-IT STUDY DESIGN

Summary

- The WEB was examined in WEB-IT, a prospective, multicenter, single-arm study to evaluate the safety and effectiveness of the WEB in patients with WNBAs.
- The primary effectiveness endpoint in WEB-IT was the proportion of patients with complete aneurysm occlusion without retreatment, without recurrent SAH, and without clinically significant (> 50%) parent artery stenosis at 12 months after treatment.
- The primary safety endpoint in WEB-IT was the proportion of patients with death of any nonaccidental cause or any major stroke within the first 30 days after treatment or major ipsilateral stroke or death due to neurologic cause from day 31 to 12 months after treatment.
- Due to limitations of currently available surgical and endovascular treatment options at the time of study initiation, the safety and effectiveness of the WEB was compared to pre-established performance thresholds:
  - An OPC of 35% for the primary effectiveness endpoint was determined based upon a comprehensive review and analysis of published results of clinical studies.
  - A PG of 20% for the primary safety endpoint was established in alignment with similar devices.

4.1 WEB-IT Study

The WEB-IT Study was a prospective, multicenter, single-arm, interventional study to determine the safety and effectiveness of the WEB for the treatment of WNBAs located in the anterior (MCA bifurcation, ICAt, or AComm) and posterior (basilar apex) circulations in adults ages 18-75. WEB-IT was conducted at 21 US and 6 international study sites in a total of 150 patients diagnosed with a WNBA in the appropriate neurovascular location.

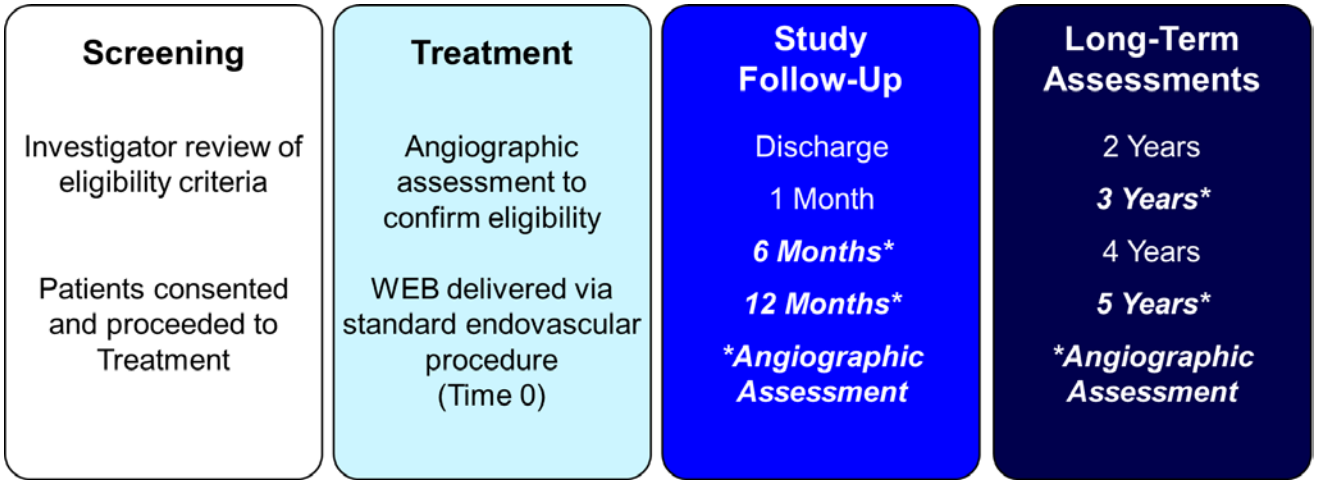
A single-arm study design that utilized an OPC to measure effectiveness and a PG for safety was considered most appropriate for WEB-IT due to limitations of the single standard of care treatment options for WBNAs. The safety and effectiveness of WEB treatment was compared to an OPC derived from a comparable subset of patients from contemporary randomized studies as well as literature cohorts in patients with similar ruptured and unruptured IAs that underwent coil embolization, stent-assisted coil embolization, or surgical clipping procedures (see Section 4.1.3.3 for more details on OPC determination).

As shown in Figure 11, WEB-IT consisted of 3 phases: Screening (Visit 1), Treatment (Visit 2), and Follow-up (Visits 3-9). Patients who met the inclusion and exclusion criteria at the Screening Visit qualified for the study and underwent a standard endovascular neurosurgical embolization procedure to deliver and implant the WEB in the WNBA at the Treatment visit. The WEB implantation was to

be performed within 30 days of baseline assessment. A detailed description of the WEB implantation procedure can be found in Section 3.2.1.

Patients with successful WEB placement entered the Follow-up Phase for 5 years ± 8 weeks. Follow-up visits were conducted at 30 days (± 7 days), 6 months (± 20 days), and 12 months (± 7 weeks). Assessments and procedures at various timepoints included: health history, physical examination, neurological examination, medication history, aneurysm information, NIHSS score, mRS score, Hunt & Hess Grade (if applicable), AE history, and angiographic imaging.

Figure 11: Schedule of Events in WEB-IT Study



4.1.1 Oversight

The study utilized an independent Core Laboratory to evaluate the angiographic results to ensure that all effectiveness evaluations were based on an unbiased assessment of the patients' imaging results. The primary role of the Core Laboratory was independent adjudication of the occlusion outcome of the index IA. A board-certified, independent interventional neuroradiologist performed all study assessments for the Core Laboratory (James Byrne, MD, FRCS, FRCR, Consultant Interventional Neuroradiologist for Oxford University Hospitals). The Core Laboratory also adjudicated the occurrence of parent artery stenosis and assessed angiographic percentage occlusion and any aneurysm recurrence defined as aneurysm growth or recanalization.

In addition, all AEs, device failures, and site reported deviations were reviewed by an independent CEA (Andrew Molyneux, MD, Sr. Clinical Research Fellow at the Nuffield Department of Surgery at the University of Oxford, UK, an honorary consultant neuroradiologist at the Oxford Radcliffe Hospitals NHS trust and the North Bristol NHS Trust). The CEA adjudicated safety data were used in all safety analyses to ensure that the safety determination is based on an unbiased assessment of the patient outcomes.

An independent DMC provided oversight during the study to ensure patient safety. The DMC comprised a multidisciplinary team of physicians and a biostatistician who had no direct communication with the sites or investigators.

The complete listing of DMC members, as well as further information on Drs. Bryne and Molyneux can be found in Appendix 11.2.

4.1.2 Key Enrollment Criteria

Patients could be included in the study if they met the following inclusion criteria:

1) Patient must be 18-75 years of age at the time of screening.
2) Patient must have a single ruptured[2] or unruptured IA requiring treatment. If the patient had an additional IA requiring treatment, the additional IA must not require treatment within 60 days of the index procedure.
3) The IA treated must have had the following characteristics:
    a. Saccular in shape
    b. Located in basilar apex, MCA bifurcation, ICAt, or AComm
    c. Dome-to-neck ratio ≥1
    d. Diameter of the IA appropriate for treatment with the WEB Aneurysm Embolization System per device Instructions for Use Wide-neck IA with neck size ≥ 4mm or dome-to-neck < 2.
4) Patient had an IA that was appropriate for treatment with WEB without the use of additional implanted devices.
5) If the IA previously ruptured, patient must be neurologically stable with Hunt & Hess Score of I or II.

Patients were excluded from the study for any of the following reasons:

1) Patient had an IA with characteristics unsuitable for endovascular treatment.
2) Microcatheter did not reach patient's index aneurysm to allow necessary access to treat with study device.
3) Patient had vessel characteristics, tortuosity or morphology which precluded safe access and support during treatment with study device.
4) Patient had vascular disease or other vascular anomaly that precluded the necessary access to the aneurysm for use of the study device.
5) Patient had clinical, angiographic or computed tomography (CT) evidence of vasospasm, vasculitis, an intracranial tumor (except small meningioma) or any other intracranial vascular malformations on presentation.

[2] For the purposes of this study, a ruptured IA patient was defined as a patient with computed tomography (CT), magnetic resonance imaging (MRI), or lumbar puncture evidence of subarachnoid hemorrhage attributed to the index aneurysm within the last 60 days.

6) Patient had conditions placing them at high risk for ischemic stroke or had exhibited ischemic symptoms such as transient ischemic attacks, minor strokes, or stroke-in-evolution within the prior 60 days.
7) Patient had any circulatory, neurovascular, cardiovascular, or neurologic conditions that resulted in unstable neurological symptoms.
8) Patient had an mRS score ≥ 2 prior to presentation or rupture (as applicable).
9) Patient had an SAH from a non-index aneurysm or any other intracranial hemorrhage within 90 days.
10) Patient had physical, neurologic or psychiatric conditions which precluded his/her ability to comply with all aspects of the screening, evaluation, treatment, and the post-procedure follow-up schedule.
11) Patient's index IA was previously treated.
12) Patient was taking anticoagulants or had a known blood dyscrasia, coagulopathy, or hemoglobinopathy.

4.1.3 Effectiveness Endpoints

4.1.3.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint was a composite endpoint of the proportion of patients with complete aneurysm occlusion without retreatment, without recurrent SAH, and without clinically significant (> 50%) parent artery stenosis at 12 months post-treatment. A patient was considered to have met the primary effectiveness endpoint upon meeting all of the above criteria.

4.1.3.2 Effectiveness Endpoints Measures

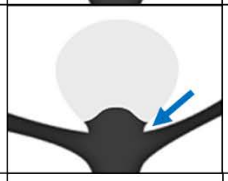
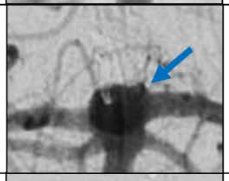
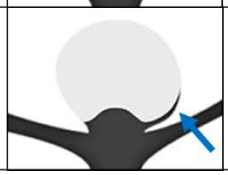
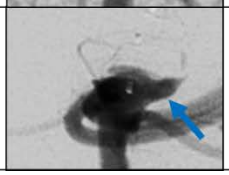
Aneurysm occlusion and parent artery stenosis were assessed based on the independent Core Laboratory evaluation of the 6- and 12-month follow-up angiograms. The 12-month angiograms were used for the primary effectiveness endpoint evaluation. Retreatment was determined based on the Investigator's reporting of the need for additional intervention at the time of the procedure or at any follow-up intervention required to treat the target aneurysm. Patients requiring retreatment of the target aneurysm within 12 months were considered failures for the primary effectiveness endpoint.

Effectiveness Assessment

Given the proximal marker recess design of the WEB, an alternative assessment tool was necessary to evaluate the effectiveness of the device. The use of alternative assessment tools for novel devices was recently discussed by the Neurologic Devices Advisory Committee Panel on March 1, 2018. The WOS was developed as the grading scale for assessment of the occlusion outcome of the index aneurysm for the primary effectiveness endpoint in WEB-IT. The WOS is a validated modification of the established Raymond Scale, which is intended for embolization coils. Like the Raymond Scale, the WOS has 3 categories, with Complete Occlusion considered a success and Residual Neck and Residual Aneurysm considered failures in WEB-IT (Figure 12). Complete occlusion in the

scale may have two angiographic signatures: 1) Complete Occlusion (not shown) and 2) Complete Occlusion with a marker recess, that is more applicable to the WEB design (shown in Figure 12)

Figure 12: The WEB Occlusion Scale

Grade	Definition	Schematic	Angiogram
Complete Occlusion	No contrast in contact with the IA neck or with the wall of the IA sac		
Residual Neck	Some contrast in contact with IA neck but no contrast in contact with wall of the IA sac or the inside of WEB device		
Residual Aneurysm	Apparent contrast in contact with the IA sac or the inside of the WEB device		

As detailed in Section 3.2, the WEB was designed with proximal and distal recesses to allow deployment of the device completely within the aneurysm sac, preventing the device from prolapsing into the parent artery and reducing the need for post-procedure dual antiplatelet therapy. In aneurysms completely occluded with the WEB, an angiographic signature of a small proximal marker recess is expected. The proximal recess of the WEB is the most secure portion of the aneurysm with the highest metal surface area coverage, thus ensuring the most robust neoendothelial overgrowth. In patients with Complete Occlusion, no contrast is seen beyond the device recess into the aneurysm, and the outcome is stable at angiographic follow-up.

Importantly, several lines of evidence have been used to validate the WOS in aneurysms treated with the WEB. Lubicz et al. (2014) first described the WOS modification of the Raymond scale in a retrospective, multicenter experience of 45 patients and its applicability to the short-term and mid-term follow-up of WEB-treated aneurysms. The authors concluded that opacification of the WEB recess can be differentiated from true neck or aneurysm remnants.

Independently, Fiorella et al. (2015) established the high interobserver validity of the scale (kappa statistic 0.779 with a 95% CI of 0.700 to 0.857), concluding that the WOS produces consistent reports of angiographic occlusion.

Finally, histopathologic validation of WOS validity was established by Rouchaud et al. (2016). A strong correlation was seen between angiographic occlusion grades and histopathological findings in this report of 80 preclinical rabbit elastase aneurysms (overall accuracy of Digital Subtraction Angiography to Histology was 82.5% with a 95% CI of 73.8% to 91.9%).

Thus, the WOS has been validated for interrater variability and histologically as a method for assessing complete occlusion in the presence of a WEB marker recess (Complete Occlusion) as

opposed to a residual neck remnant. Additionally, peer-reviewed clinical studies have confirmed the detection of a marker recess versus a neck remnant.

Parent Artery Stenosis

Parent artery stenosis was defined as a reduction at follow-up angiogram from pre-treatment images in parent artery diameter just proximal or distal to the treated index aneurysm. Parent artery stenosis was graded according to the scale in Table 11.

Table 11: Definition of Parent Artery Stenosis Grade

Grade	Term	Definition
0	None	No reduction in parent artery diameter immediately proximal or distal to the index IA compared to baseline images
1	0-50%	More than 0% but less than or equal to 50% reduction in parent artery diameter immediately proximal or distal to the index IA compared to baseline images
2	>50-100%	More than 50% but less than or equal to 100% reduction in parent artery diameter immediately proximal or distal to the index IA compared to baseline images

4.1.3.3 Objective Performance Criterion

The primary effectiveness success rate at 12 months was compared to an OPC established from the relevant literature. This OPC was derived as the lower two-sided 95% confidence limit of the adjusted mean rate of complete occlusion from data obtained from a meta-analysis of available comparable data as well as relevant surgical and endovascular clinical literature on patients with WNBAs, adjusted for the anticipated mix of aneurysm locations (anterior or posterior) to be encountered in the study. Details on the methods used to derive the OPC can be found in Appendix 11.3.1.

The derived adjusted mean (± standard error [SE]) rate of complete occlusion from the updated meta-analysis was 50% ± 8%, and the corresponding lower two-sided 95% confidence limit of the adjusted mean was 35%. Thus, the prespecified OPC was defined as a success rate significantly greater than 35%.

To ensure that the original OPC derived in 2014 was still relevant at the time of PMA submission, the analyses were repeated in 2017 using updated literature to reflect the current rates for the most successful treatment modality. Details on the methods to update the OPC can be found in Appendix 11.3.2. The derived adjusted mean (± SE) rate of complete occlusion from the updated meta-analysis was 53% ± 7%, and the corresponding lower two-sided 95% confidence limit of the adjusted mean was 39%. This rate shows that the original OPC of 35% is still a valid threshold for comparison.

A recent peer-reviewed meta-analysis of literature related to the treatment of WNBAs reported a Core Laboratory adjusted OPC of 39.3% (Fiorella et al. 2017). Additional support for the identified OPC for WEB-IT comes from the BRANCH Study published in 2018 (De Leacy et al. 2018). This independent, retrospective, multicenter study of 115 unruptured WNBAs of the MCA or basilar apex treated using currently available devices reported a Core Laboratory adjudicated complete occlusion rate of 30.6% with a lower 95% CI of 22% at 1-year follow-up.

4.1.3.4 Secondary Effectiveness Endpoint

The secondary effectiveness endpoint was the proportion of patients with angiographic aneurysmal recurrence, defined as aneurysm growth or recanalization at 12 months after treatment. Assessment of this endpoint was also performed by the Core Laboratory.

4.1.3.5 Additional Effectiveness Endpoint

An additional prespecified endpoint was adequate occlusion, defined as the proportion of patients achieving Complete Occlusion or Neck Remnant.

4.1.4 Safety Endpoints

4.1.4.1 Primary Safety Endpoint

The primary safety endpoint in WEB-IT was the proportion of patients with death of any nonaccidental cause or any major stroke (defined as a stroke, which increases the NIH Stroke Scale by > 4 at the time of assessment AND which remains present after 7 days) within the first 30 days after treatment or major ipsilateral stroke or death due to neurologic cause from day 31 to 12 months after treatment. A patient was considered a safety failure upon meeting any of these criteria.

4.1.4.2 Performance Goals

As no prospective clinical study has focused specifically on the rates of major stroke or death in patients with WNBAs, the Sponsor conducted a literature review to establish a threshold for comparison (see Appendix 11.3). A safety PG was originally derived from the rates of primary safety events reported in a meta-analysis of the clinical literature for endovascular and surgical methods of treatment of bifurcation and wide neck IAs. Based on this analysis, the upper two-sided 90% CI was 25.8%. The Agency advised the Sponsor that, for similar devices, a safety PG be defined as the upper limit of the 95% confidence interval being less than 20%. For reference, in approved marketing applications of similar devices (e.g. Pipeline, LVIS, & Surpass), a primary safety PG of 20% was used.

4.1.4.3 Additional Safety Endpoints

Additional safety endpoints included mortality at 30 days, 6 months, and 12 months, and morbidity defined as the proportion of patients with an mRS score > 2. The mRS is a clinician-reported measure of global disability to evaluate stroke patient outcomes. The mRS is a 7-point scale (Rankin 1957):

- 0 = No symptoms at all
- 1 = No significant disability despite symptoms; able to carry out all usual duties and activities
- 2 = Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
- 3 = Moderate disability; requiring some help, but able to walk without assistance

- 4 = Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
- 5 = Severe disability; bedridden, incontinent and requiring constant nursing care and attention
- 6 = Dead

4.1.5 Statistical Analyses

Both the primary effectiveness and primary safety endpoint hypotheses had to be satisfied for the study to be considered successful. A patient was considered a success on the primary effectiveness endpoint upon meeting all of the criteria: complete aneurysm occlusion without retreatment, without recurrent SAH, and without clinically significant (> 50% stenosis) parent artery stenosis at 12 months after treatment as assessed by the Core Laboratory. A patient was considered a failure on the primary safety endpoint if any of the criteria were met: death of any nonaccidental cause or any major stroke (defined as a stroke, which increases the NIH Stroke Scale by > 4 at the time of assessment AND which remains present after 7 days) within the first 30 days after treatment or major ipsilateral stroke or death due to neurologic cause from day 31 to 12 months after treatment.

The secondary and additional effectiveness and safety endpoints were prespecified but did not have planned hypotheses and were not adjusted for multiplicity.

4.1.5.1 Missing Data

For the primary analysis, patients whose data were not missing at random, such as those who exited the study due to a device-related primary safety event, were imputed as both a safety and effectiveness failure. Patients who required adjunctive devices (other than balloons) were also considered failures for the primary effectiveness endpoint. For patients in whom the placement of the device failed (ie, no implant placed), the final safety endpoint was the 30-day follow-up visit.

Patients with missing data who exited the study due to a non-device-related primary safety event were considered a failure for the safety endpoint. The effectiveness endpoint for these patients was imputed using multiple imputations with random selection from patients with outcomes with similar aneurysm locations, rupture status and if indicated, aneurysm size, and 6-month outcome (if available). If there were marked differences in the responses from geographical locations, this was also used to sub-group patients for the sampling frame.

Withdrawn patients' missing outcomes for the primary safety endpoint composite were included in the safety composite and assumed to be MAR if they withdrew from the study for any reason not associated with a primary safety event. A multiple imputation similar to effectiveness was used to address missing data for the safety endpoint.

4.1.5.2 Analysis Populations

The **Intent to Treat (ITT) Population** included every patient that was consented, passed both clinical and angiographic eligibility criteria, and in whom there was an attempt to place a WEB device. The primary safety and effectiveness analyses were performed on this population. As shown in Table 12, the ITT Population in WEB-IT comprised 150 patients.

The **Completed Cases (CC) Population** included the group of ITT patients who have complete endpoint data for the endpoint of interest. For the primary effectiveness endpoint analysis, the CC Population included all patients with angiographic assessment by the Core Laboratory at 1-year follow-up sufficient to allow assessment of both complete aneurysm occlusion and clinically significant (> 50%) parent artery stenosis. Patients known to be failures due to procedure failure, retreatment, or recurrent SAH were included in the analysis as failures regardless of the availability of 1-year assessment. The CC Population in WEB-IT included 143 patients (Table 12).

For the primary safety endpoint analysis, the CC Population included all patients with an assessment sufficient to evaluate the presence or absence of the primary safety endpoints or in whom a primary safety endpoint event occurred prior to the 1-year assessment. Supportive analyses of the primary safety and effectiveness endpoints were completed with this population including multivariable analyses. In addition, secondary effectiveness endpoints were evaluated in the CC Population.

The **Per-Protocol (PP) Population** included all CC cases who additionally meet all study eligibility criteria and did not have a major protocol deviation that might affect the primary endpoint. In WEB-IT, the CC and PP Populations were identical with 143 patients (Table 12).

Table 12: Analysis Populations in WEB-IT

	N	Definition
Enrolled, Intent to Treat (ITT)	150	All enrolled patients / device implant attempted
Complete Case (CC)	143	ITT patients with 12-month evaluation
Per Protocol (PP)	143	Complete case patients without protocol deviation

4.1.5.3 Poolability of Data

An analysis within and across geographic locations (US or outside the US) was conducted to ensure poolability of study data. Study sites with fewer than 6 patients were combined into pseudo-sites. Pseudo-sites were used for all multivariate analyses including the analysis to determine pseudo-site or geographic region heterogeneity in primary endpoint response for pooling. This poolability analysis did not identify any baseline characteristic evaluated that impacted the primary effectiveness results either by center (p=0.42) or by US vs non-US (p=0.86).

5 WEB-IT EFFECTIVENESS RESULTS

Summary

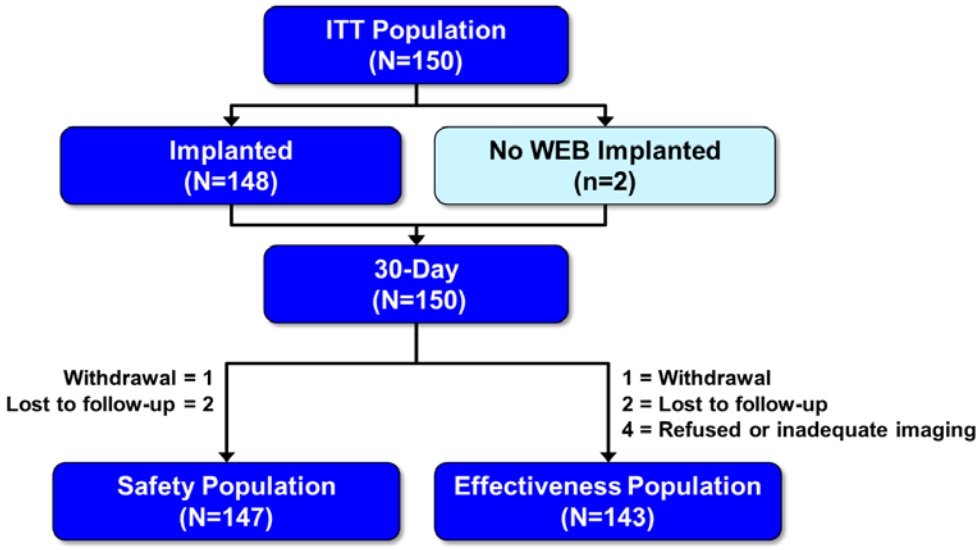
- Baseline demographics and medical characteristics in WEB-IT were representative of the patient population that presents with IAs in a clinical setting.
- Procedure characteristics were reflective of the unique WEB design and represent a benefit to patients over other treatment options; mean total WEB procedure time was 21 minutes, with a mean of 30 minutes total fluoroscopy time.
- WEB-IT met the primary effectiveness endpoint, with 54.8% of patients achieving complete occlusion without retreatment, without recurrent SAH, and without clinically significant (> 50%) parent artery stenosis at 12 months. The lower one-sided 95% confidence limit of 48.0% was statistically significantly greater than the prespecified OPC of 35% ($p < 0.0001$).
- No subgroup, including variables that were out of balance across pseudo-sites or regions, had a statistically significant impact on the primary endpoint.

5.1 Study Population

5.1.1 Patient Disposition

Patient disposition in WEB-IT is summarized in Figure 13. A total of 179 patients were consented for possible participation in WEB-IT, and 150 passed the angiographic screening, were enrolled in the study, and underwent attempted treatment with the WEB. All 150 patients had a WEB inserted with the intention to implant and are included in the ITT Population. Of these patients, 148 had a WEB successfully implanted. The 2 patients who did not have a WEB implanted had no reported AEs and were followed per protocol through the 30-day follow-up for a final safety endpoint evaluation and then discontinued from the study. Both of these patients are considered effectiveness failures. One other patient was unable to schedule further follow up and exited the study prior to the 12-month follow-up.

Figure 13: Patient Disposition through 12 months Follow-up in WEB-IT



Of the 150 patients enrolled in the study, 136 were determined to be complete cases with valid 12-month assessments. Seven patients did not have adequate imaging to assess the aneurysm occlusion or parent artery stenosis. These 7 patients without 12-month assessment were considered MAR and had their primary effectiveness endpoint outcome imputed as explained in Section 4.1.5.1. An additional 7 patients were imputed as failures due to failed device placement (n=2), use of adjunctive device at time of procedure (n=2), or index aneurysm retreatment or planned retreatment prior to 12 months (n=3).

5.1.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics are summarized in Table 13. In the ITT Population, the mean age at treatment was 59 years, and 73.3% were female. The majority (84.5%) of patients were White, with an additional 12.1% African American and 3.4% Asian.

A total of 9 patients presented with ruptured aneurysms (6.0%). The hemorrhage severity of 6 patients was assessed as Hunt & Hess Grade 1, and the hemorrhage severity of 3 patients was assessed as Hunt & Hess Grade 2. The remaining 141 presented symptomatically or were found incidentally. Of the 141 unruptured aneurysms, the majority (80.9%) had baseline mRS scores of 0. Eighteen patients (12.0%) had a history of ischemic stroke, and 10 (6.7%), had a history of hemorrhagic stroke. Over 97% of patients with unruptured aneurysms had baseline NIHSS 0 (90%) or 1 (7.3%).

Overall, the enrollment in WEB-IT reflects the epidemiological pattern of distribution of WNBAs and their specific sizes and locations in the population of patients treated with WBNA. In WEB-IT, 91 (60.7%) were located in the anterior cerebral circulation (MCA, ICA, AComm) and 59 (39.3%) in the posterior cerebral circulation (basilar). The mean maximum sac width was 6.4 mm with a range of 3.6 to 11.4 mm. The mean maximum neck width was 4.8 mm with a range of 2.0 to 8.2 mm, and the mean maximum dome to neck ratio was 1.3 with a range of 1.0 to 2.0. The baseline

measurements of the index aneurysms were consistent with the population of patients undergoing treatment of IAs.

Table 13: Baseline Demographics and Characteristics in WEB-IT

Characteristic	WEB-IT Study N=150
Mean (SD)	
Age	58.98 (10.16)
Index Aneurysm - Maximum Sac Width (mm)	6.35 (1.55)
Index Aneurysm - Maximum Neck Width (mm)	4.75 (1.13)
Index Aneurysm - Max Dome-to-Neck Ratio	1.3365 (0.2474)
x/n (%)	
Sex (Male)	40/150 (26.67)
Race[a]	
Asian	4/116 (3.45)
Black or African American	14/116 (12.07)
White	98/116 (84.48)
Ethnicity[a]	
Hispanic or Latino	2/116 (1.72)
Not Hispanic or Latino	114/116 (98.28)
Prior Rupture	9/150 (6.00)
Hunt & Hess (ruptured only)	
I	6/9 (66.67)
II	3/9 (33.33)
Unruptured Discovered by	
Symptomatic	33/141 (23.40)
Incidental	108/141 (76.60)
Current or Former Smoker	
Current	66/150 (44.00)
Former	32/150 (21.33)
Non-Smoker	52/150 (34.67)
Visual Disturbance	26/150 (17.33)
Motor Disturbance	13/150 (8.67)
Aneurysm Location	
AComm	40/150 (26.67)
Basilar	59/150 (39.33)
ICA	6/150 (4.00)
MCA	45/150 (30.00)
Previous Ischemic Stroke	18/150 (12.00)
Previous Hemorrhagic Stroke	10/150 (6.67)
NIHHS at Baseline	
0	135/150 (90.00)
1	11/150 (7.33)
2	2/150 (1.33)
5	1/150 (0.67)
6	1/150 (0.67)
mRS (unruptured)	
0	114/141 (80.85)
1	27/141 (19.15)

[a]Race and Ethnicity were not obtained for patients from the European and Canadian sites.

5.2 Procedure Outcomes

Procedure Times

A total of 148 patients received a WEB via a single endovascular neurosurgical procedure. Information about the implantation procedures in WEB-IT is presented in Table 14. Procedure time was defined as the time the WEB was inserted into the microcatheter at the puncture site to the time the WEB delivery system was removed from the catheter. The mean procedure time was approximately 21 minutes, and the median time was approximately 16 minutes.

WEB deployment time was defined as the time the WEB was inserted into the microcatheter at the puncture site to the time when the WEB was detached. The mean WEB deployment time was approximately 18 minutes.

The mean fluoroscopy time was approximately 30 minutes, and the mean total fluoroscopy radiation dose was 2,756.31 mGy (37.2 mGy/kg). It is notable that the WEB-IT study protocol required additional imaging runs, thus fluoroscopy times would likely be even shorter in a clinical use setting.

Table 14: WEB Implantation Procedure Information in WEB-IT

Procedure Data	Mean (SD) N=148
WEB Deployment Time (min)	18.04 (20.57)
Total WEB Procedure Time (min)	20.91 (21.23)
Total Fluoroscopy time (min)	30.15 (15.68)
Total Fluoroscopy Dose (mGy)	2756.31 (2582.44)
Fluoroscopy (mGy/kg)	37.20 (35.43)

Technical Success

In WEB-IT, technical success was defined in 2 ways:

a) Successful implantation of a WEB device in the index aneurysm during the index procedure
b) Successful implantation without the need for unapproved adjunctive implantable devices (ie, coils, stents, and flow diverters)

Table 15 displays the technical success rates according to each definition. Technical success (a) was achieved in 98.7% of patients (148/150). Two patients were unable to be implanted with the WEB due to vessel tortuosity precluding the ability to maintain catheter position during delivery of the device in 1 patient and unavailability of a smaller device size after initial attempt with a larger device size in the other patient.

Technical success (b) was achieved in 97.3% of patients (146/150). In addition to the 2 patients unable to be implanted, 2 patients required the use of adjunctive implantable devices (stents). Adjunctive balloons, allowed under the study protocol, were also used in 5 cases to assist in positioning of the WEB.

Table 15: Technical Success Rates in WEB-IT

Event	Rate n/N (%)
Technical Success[a]	148/150 (98.67)
Technical Success[b]	146/150 (97.33)
Adjunctive Devices Used	7/148 (4.73)
Balloon (Acceptable under Protocol)	5/148 (3.38)
Coils (Unacceptable under Protocol)	0/148 (0.00)
Stent (Unacceptable under Protocol)	2/148 (1.35)
Flow Diverter (Unacceptable under Protocol)	0/148 (0.00)

[a]Successful implantation of the WEB device during the index procedure.
[b]Successful implantation of the WEB device with implantable adjunctive device use during the index procedure as failures.

Device Attempts

For the 150 patients in whom device placement was attempted, a total of 211 device attempts resulted in 148 device placements (Table 16). A total of 63 inserted devices were not implanted, and 89% of the devices that were not implanted (56 devices) were related to the decision by the Investigator that an alternative size was preferred. In all but 1 instance, a correctly sized device was ultimately successfully implanted. If the Investigator determined that an alternative size device may result in a better outcome for the patient, the WEB was retracted back into the delivery catheter and an alternate device was advanced and deployed. Exchange of devices for an alternate size did not result in any clinical sequelae.

In 6 of the 7 other cases in which a WEB was removed for a reason other than sizing, another WEB device was successfully implanted in the target aneurysm.

Table 16: WEB Implantation Disposition in WEB-IT

Disposition	Number of Devices n/N (%)
Inserted	211 (100.00)
Not Implanted	63 (29.86)
Improper Size	56/63 (88.88)
Other	7/63 (11.11)
Implanted	148/211 (70.14)

The device was not implanted on the first attempt in 50 patients (Table 17). All but 1 of these patients had successful implantation with an additional device. Patients with 3 or 4 WEB implantation attempts did not demonstrate additional safety risks compared to those with 1 or 2 attempts.

Table 17: Number of Attempts to Implant WEB in WEB-IT

Number of Attempts	n (%) N=150
1	100 (66.67)
2	40 (26.67)
3	9 (6.00)
4	1 (0.67)

It is important to note that, like coils, the WEB System was explicitly designed to allow physicians to choose from several WEB sizes that, within reason, will all deploy safely into an aneurysm. When the physician is fully satisfied with the size and result of WEB deployment, he or she detaches the WEB from the deployment system.

5.3 Primary Effectiveness Endpoint

As shown in Table 18, 54.8% of patients met the success criteria with the combined analysis of imputations for missing patients. The significance level for the one-sided hypothesis test that the primary effectiveness endpoint event rate was greater than the pre-established OPC of 35% was $p < 0.0001$, demonstrating that the success criterion for the primary effectiveness endpoint was met. The lower limit of the two-sided 90% CI (one-sided 95% CI) of 48.0% far exceeds the 35% OPC for effectiveness.

Table 18: Primary Endpoint Imputation and Analysis in WEB-IT

Source	Patient Successes % (SE)	One-sided 95% Lower Confidence Limit	P-value[c]
All Imputations Combined[a]	54.8 (4.1)	48.0	**<0.0001**
CC/PP	77/143 (53.9)	46.6	**<0.0001**

[a]Twenty imputations are combined into a single inference by the method of Rubin (1987) that includes within and between imputation variation.
[c]P-value from a one-sided exact binomial test at alpha =0.05.

The primary effectiveness endpoint success rate for the CC/PP Population was 53.9% (77/143) with a lower limit for the two-sided 90% CI of 46.6%. In all cases of imputation and for the CC/PP analyses, the significance level for the one-sided hypothesis test that the primary effectiveness endpoint event rate was greater than 35% (the pre-established OPC) was $p < 0.0001$.

5.3.1 Endpoint Components

The components of the primary endpoint in the CC/PP Population are shown in Table 18. In the CC/PP Population, 77/143 (53.9%) achieved complete aneurysm occlusion at the 12-month follow-up. This component contributed primarily to the combined endpoint success rate.

The development of a significant parent artery stenosis (> 50%) was not observed in any patient with complete occlusion. These data confirm that the WEB device and its placement do not contribute to the development of a new stenosis in the parent artery of the aneurysms being treated.

With regard to aneurysm retreatment, 5.6% of the CC/PP Population (8 patients of the 143 CC/PP cases) underwent or had planned target aneurysm retreatment through 378 days.

There were no recurrent SAH events during the study among the patients presenting with ruptured aneurysms at baseline.

Additionally, a prespecified additional analysis of adequate occlusion, defined as the proportion of patients achieving Complete Occlusion or Neck Remnant, showed that 83.2% of patients in the CC/PP Population achieved adequate occlusion at 12 months.

Table 19: Primary Effectiveness Endpoint Component Analysis in the Completed Cases in WEB-IT

Component	Number of Patients n (%) N=143
Primary Endpoint Success	77 (53.9)
With imaging without imputation in CC	136 (95.1)
Imputed as failure for CC	7 (4.9)
Aneurysm Occlusion	
Complete	77[b] (53.9)
Residual Neck	44 (30.8)
Residual Aneurysm	15 (15.4)
Imputed as Failure for Primary Effectiveness	7 (4.9)
Parent Vessel Stenosis	
None	128[c] (89.5)
≤ 50%	7[d] (4.9)
> 50%	1[e] (0.7)
Imputed as Failure for Primary Effectiveness	7 (4.9)
Adjunctive Device (Imputed as failure)	2 (1.4)
Failure to Implant (Imputed as failure)	2 (1.4)
Retreatment of index aneurysm[a] (Imputed as failure)	3 (2.1)
Recurrent Subarachnoid Haemorrhage	0 (0.0)

[a]There were 8 patients who had retreatment but 5 of those were failures on the 12-month angiogram, so these patients were counted under their angiogram events. For the 3 patients in this row, 1 had a 12-month result that was a complete occlusion (b) (4) and 2 did not have a 12-month outcome recorded.

[b]There were 81 patients with complete occlusion at 12 months but 4 must be deleted because of retreatment, adjunct stent use during the procedure, or missing 12-month parent vessel score.

[c]There were 130 patients with no parent vessel incursion but 2 of them had adjunct stent use during the procedure.

[d]There were 8 patients with parent vessel stenosis of less than or equal to 50% but 1 was a patient scheduled at 12 months for retreatment.

[e]This patient had parent artery stenosis after retreatment which is included here for completeness but was considered a failure for incomplete occlusion at 12 months.

5.3.2 Sensitivity Analyses

To demonstrate the robust nature of this unbiased imputation, a tipping point analysis was conducted using all possible outcomes of the imputed results moving from "worst case" to "best" case scenarios. In all cases, the significance level was < 0.0001, well below the 0.05 required for study success, and the lower one-sided 95% confidence limit was above 35%.

5.4 Secondary Effectiveness Endpoint

The secondary effectiveness endpoint was the proportion of patients with angiographic aneurysmal recurrence defined as aneurysm growth or recanalization at 12 months after treatment. A total of 18 patients (12.6%) had aneurysmal recurrence: 17 patients had recanalization of the original aneurysm without growth or expansion, and 1 patient had regrowth (or new growth or expansion of the aneurysm after treatment). Of the 17 with recanalization, 12 remain adequately occluded with residual necks and 5 had residual aneurysms.

5.5 Subgroup Analyses

Subgroup analyses were conducted on the primary effectiveness endpoint for variables including age, sex, aneurysm location, aneurysm rupture status, and geographical location, and no statistically significant differences were seen across subgroups. All point estimates fell above the pre-specified 35% success criteria, showing a consistent benefit of the WEB across all analyzed subgroups (Table 20 and Figure 14).

Additional analyses of the primary effectiveness endpoint success rate across each diameter of the WEB size implanted and the types of catheters used showed no statistically significant differences. The proportions of patients successful for the primary effectiveness endpoint did not differ significantly across aneurysm locations (Figure 15), showing that there was no subgroup of patients based on aneurysm location who benefited more than others from treatment with the WEB in WEB-IT. It is important to note that WEB-IT was not powered to show a difference by subgroup, and sample sizes are small in some subgroups.

Table 20: Subgroup Analyses of the Primary Effectiveness Endpoint in the CC/PP Population in WEB-IT

Characteristic	n/N (%)
Sex	
Male	21/37 (56.8)
Female	56/106 (52.8)
Age	
< 65	51/94 (54.3)
≥ 65	26/49 (53.1)
Race	
White	50/92 (54.4)
Non-White	9/17 (52.9)
Ethnicity	
Hispanic	1/2 (50.0)
Non-Hispanic	58/107 (54.2)
Sac Width	
< 8 mm	64/118 (54.2)
≥ 8 mm	13/25 (52.0)
Aneurysm Status	
Ruptured	4/8 (50.0)
Unruptured	73/135 (54.1)
Aneurysm Location	
Posterior	34/58 (58.6)
Anterior	43/85 (50.6)
Clinician experience	
1-3	16/29 (55.2)
4-6	17/41 (41.5)
> 6	44/73 (60.3)

Figure 14: Primary Effectiveness Endpoint Results by Baseline Demographics and Aneurysm Characteristics in WEB-IT

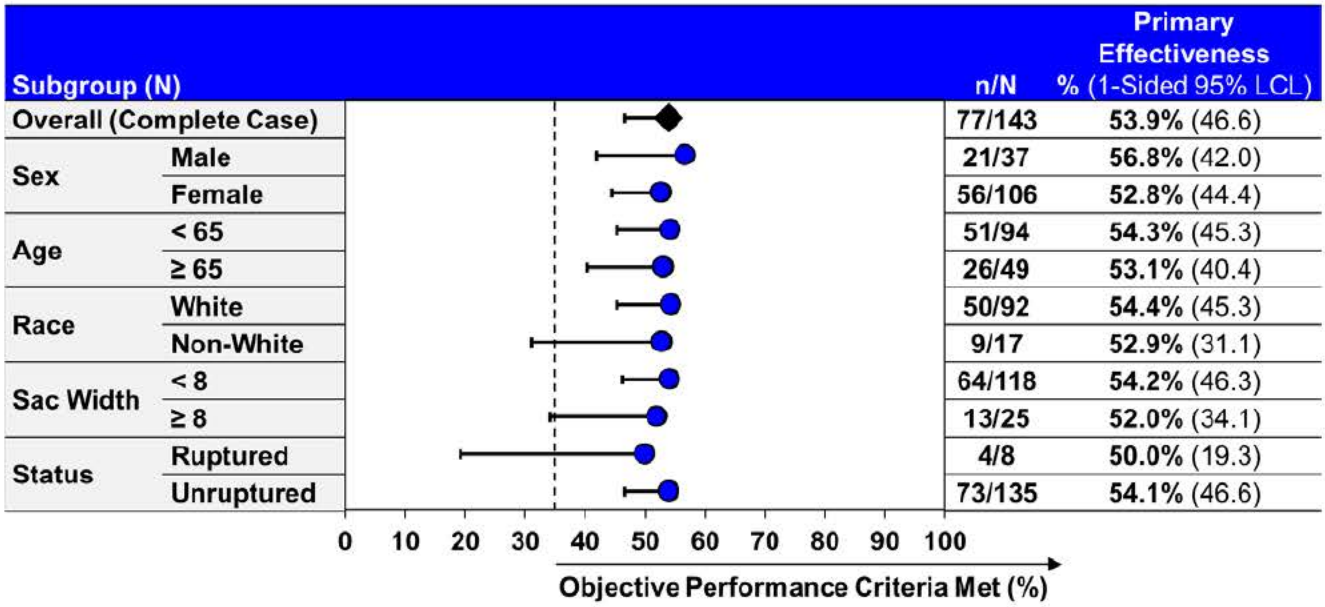
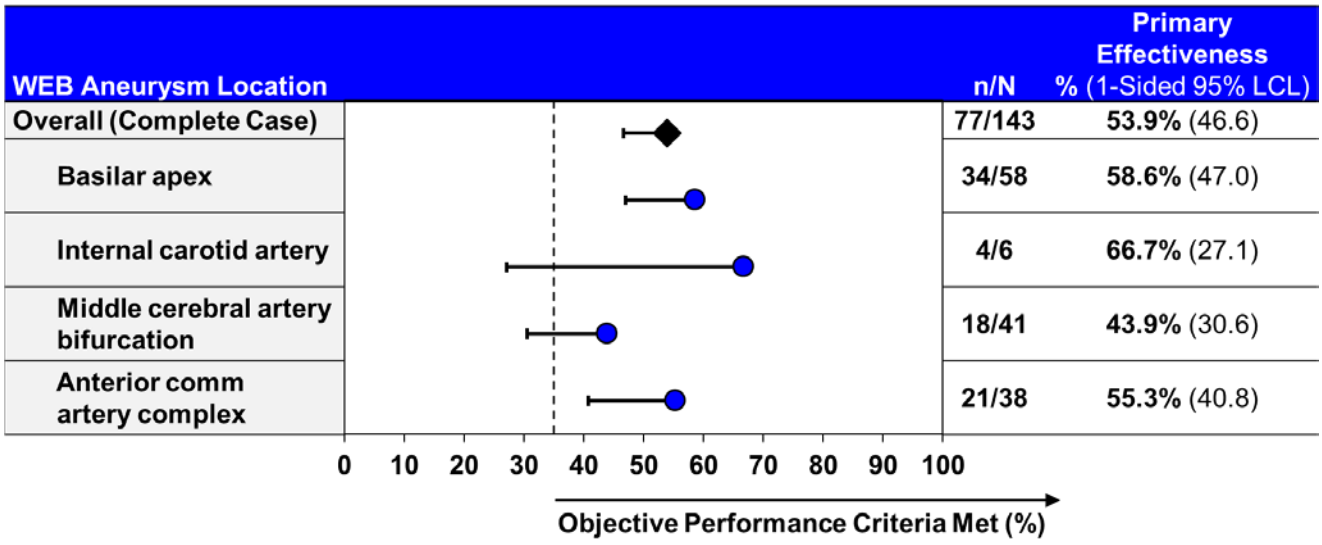


Figure 15: Primary Effectiveness Endpoint Results by Aneurysm Location in WEB-IT



6 CLINICAL SAFETY

Summary

- WEB-IT met its primary safety endpoint with an event rate of 0.67% at 12 months in the ITT Population, which was significantly lower than the prespecified PG of 20% ($p < 0.0001$).
- The single primary safety endpoint event was a major stroke within the first 30 days of WEB implantation; there were no reported deaths through 12 months, and no major ipsilateral strokes between day 31 and 12 months.
- Within the first 30 days, 45% of patients experienced non-serious AEs, most commonly headache (13%), nausea (6%), and adverse drug reaction (5%).
- Between day 31 and 12 months, 43% of patients experienced non-serious AEs, most commonly headache (13%), adverse drug reaction (5%), and hypertension (2%).
- Within the first 30 days, 14% of patients experienced SAEs: 7% were procedure-related, 1% were device-related, and 2% were procedure- and device-related.
- A total of 11 minor ischemic stroke events and 4 hemorrhagic stroke events (1 major) occurred in 13 patients.
- Overall, the WEB and the implantation procedure were found to be safe for patients with WNBAs.

6.1 Safety Population

A total of 150 patients were enrolled in the WEB-IT study, and 148 had the WEB device implanted. All 150 patients are included in the safety analyses.

Complete follow-up through 12 months (or 30 days for the 2 patients in whom a WEB device was not implanted) was obtained in 145 of the 150 patients. Of the 5 patients without complete follow-up through 12 months, 2 were confirmed to be alive and stroke free at 12 months, and the remaining 3 had 30-day follow-up visits and were alive and stroke free at that time. One of the 3 patients was documented to be alive without a history of stroke beyond 2 years based on an emergency admission for a non-neurologic reason. Conservatively, this patient was considered to be missing at 12 months for purposes of the primary safety endpoint analysis.

6.2 Primary Safety Endpoint

In WEB-IT, 1 patient (0.67%) in the ITT Population had a primary safety event (Table 21). The primary safety endpoint rate was statistically significantly lower than the PG of 20% ($p < 0.0001$). In addition, the upper one-sided 95% confidence limit of 6.04% in the ITT analysis was well below the 20% threshold. For the ITT analysis of primary safety, similar to the imputation for the primary effectiveness endpoint, the 3 patients without a 12-month safety determination were imputed by grouping the missing patients by aneurysm location and rupture status.

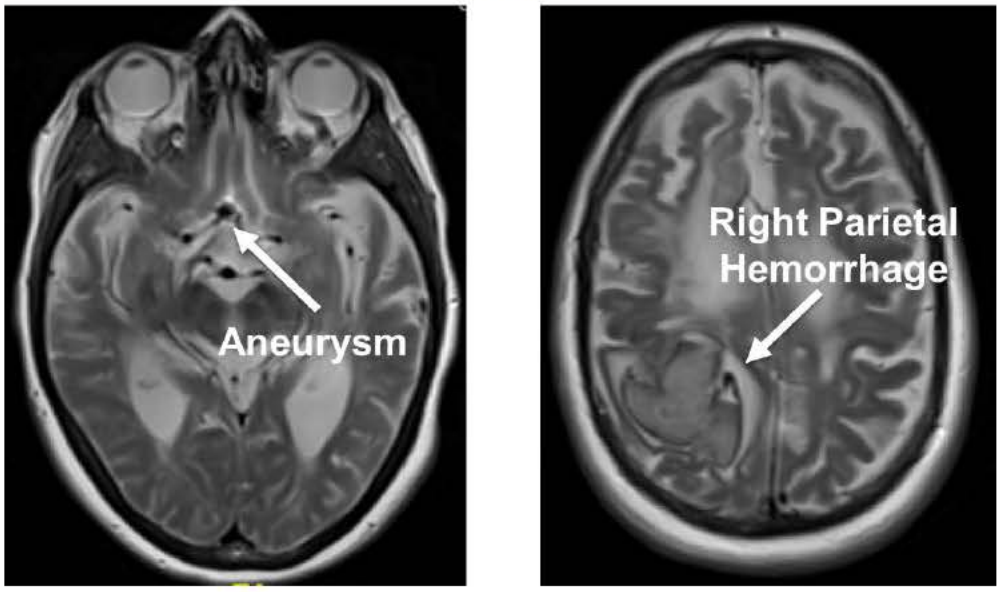
Table 21: WEB-IT Primary Safety Endpoint Analysis

Source	Patient Event (%) (SE)	One-sided 95% Upper Confidence Limit[b]	P-value[c]
All imputations combined[a]	0.67 (3.27)	6.04	< 0.0001

a Twenty imputations are combined into a single inference by the method of Rubin (1987) that includes within and between imputation variation.
b When stated as a percent, this value corresponds to the one-sided 95% upper confidence limit that must be smaller than 20% to reject the null primary endpoint hypothesis.
c P-value from a one-sided exact binomial test at alpha =0.05.

The single primary safety endpoint event, a SAH adjudicated as a major stroke, occurred in a patient on post-procedure day 22. The location of the SAH was ipsilateral but remote from the target aneurysm (Figure 16). This patient was a 54-year-old, non-Hispanic, Caucasian woman with Gastroesophageal Reflux Disease, Multiple Sclerosis, urinary incontinence, depression, a current smoker, and no history of a previous stroke. At baseline, the patient's aneurysm was unruptured, in the anterior communicating artery, and with a sac width of 7.4 mm and NIHSS and mRS scores of 0. The patient presented to the emergency room with a sudden onset of headache and left-sided hemiplegia 22 days following the WEB procedure. A CT scan and subsequent MRI demonstrated a new right parenchymal hemorrhage with an associated SAH. The event was characterized as a primary safety event probably related to the index procedure and/or concurrent condition. The patient had an NIHSS score of 13 on day 30, 7 days post-event. At 12 months, the patient had an mRS score of 4 due to residual left hemiplegia. The patient's aneurysm was completely occluded with no stenosis of the parent artery; the patient was therefore considered a primary effectiveness endpoint success and a primary safety endpoint failure.

Figure 16: Images of Primary Safety Event in WEB-IT



For the CC/PP analysis, the rate of a primary safety endpoint event was 0.68% with an upper limit of the two-sided 90% CI (one-sided 95% CI) of 3.19%, which is well below the prespecified threshold PG of 20%.

Table 22: Primary Safety Composite Endpoint Analysis in the CC/PP Population in WEB-IT

Endpoint	Rate	One-Sided 95% Upper Confidence Limit[a]	P-value[a]
Composite	1/147[b] (0.68)	3.19	<0.0001
Death within 30 days	0/147[b] (0.68)	2.02	<0.0001
Major Stroke within 30 days	1/147[b] (0.68)	3.19	<0.0001
Major Ipsilateral Stroke Day 31 to 12 Months	0/147[b] (0.00)	2.02	--
Neurological Death Day 31 to 12 Months	0/147[b] (0.00)	2.02	--

[a]To be compared to 0.20. The upper limit of the one-sided 95% CI needs to be less than 0.20 and the test provides the P-value for a test of the observed rate versus a performance goal rate of 0.20.
[b]There were 147 patients with 12-month evaluation of the safety endpoint.

6.3 Additional Safety Endpoints

6.3.1 Mortality at 30 days, 6 months, and 12 months

There were no deaths through 12 months in WEB-IT.

6.3.2 Morbidity (mRS > 2)

Morbidity, defined as the proportion of patients with mRS scores > 2, was 1.4% at 12 months. None of the 9 patients with ruptured aneurysms had mRS scores > 2 at 12 months. The majority of patients with unruptured aneurysms had mRS scores of 0 (111 patients) or maintained at an mRS score of 1 (13 patients) at 12 months; 2 patients with unruptured aneurysms had mRS scores > 2 at 12 months.

Table 23: Patient Morbidity (mRS > 2) at 12 months in WEB-IT

	Time Point			
	Discharge n/N (%)	30 Days n/N (%)	6 Months n/N (%)	12 Months n/N (%)
mRS > 2	1/150 (0.67)	1/150 (0.67)	1/142 (0.70)	2/143 (1.40)

6.3.2.1 Change from Baseline in mRS Scores

An analysis of the change in mRS score at 12 months compared to baseline was conducted for all patients (n=150) treated in the clinical study (Table 23). The analysis utilized a worst-case approximation for patients with unknown or missing 12-month mRS scores (n=7) with last available score for mRS used.

Based upon this analysis, 1 additional patient was noted to have a decline in mRS score over baseline as compared to the original analysis which identified 11 patients. This conservative analysis showed in an increase in mRS score for 12 of the 150 patients compared with baseline. Of these, the scores of 10 patients had increased by 1 point, 1 patient had increased by 2 points, and 1 patient had increased by 4 points.

Table 24: mRS Change from Baseline to 12 Months in WEB-IT

mRS Score at Baseline	mRS Score at 12-Months N = 150				Total
	0 n (%)[a]	1 n (%)[a]	3 n (%)[a]	4 n (%)[a]	
0	108 (90.76)	10 (8.40)	0 (0.00)	1 (0.84)	119
1	14 (45.16)	16 (51.61)	1 (3.23)	0 (0.003)	31
Total	122 (81.33)	26 (17.33)	1 (0.67)	1 (0.67)	150[b]

[a] Percent of the row total.

[b] Two patients did not have 12-month scores but did have 6-month scores that were used as 12-month scores for this analysis. Two patients did not have an mRS at 12 months who discontinue because of no implanted device were given the 30-day scores considered to be attributable to study participation. The 3 patients with no score after 30 days were assigned their 30-day score.

It is important to note that the mRS score is not fully suitable as an objective measure of aneurysm treatment because of the potential confounding effect of other conditions that may affect the patient's disability level (FDA Neurological Devices Panel of the Medical Devices Advisory Committee Meeting, March 1, 2018). Specifically, of the 10 mRS scores that increased by 1 point:

- 2 occurred in patients with minor ischemic strokes
- 3 occurred in patients with minor ischemic strokes unrelated to the procedure or device
- 5 occurred in patients with unrelated non-neurological conditions, such as visual impairment unrelated to treatment, dizziness unrelated to treatment, ongoing muscle spasms, and arthralgia.

In addition, 1 patient's mRS score that increased by 2 points was associated with worsening baseline cerebrovascular disease unrelated to the device or procedure, and 1 patient's score increased by 4 points due to her major primary safety endpoint event.

After treatment with the WEB, 138 out of the 150 treated patients (83%) had an improved or unchanged mRS score at 12 months. Specifically:

- 14 patients had an improvement (lower score) of 1 point (to mRS 0) from baseline to 12 months.
- 12 out of the 150 treated patients demonstrated a decline (higher score) over baseline in mRS score. As described above, these declines were primarily 1 point (10/12) and were associated with events unrelated to the device or procedure in 9/12 cases.

Overall, the majority of patients had a favorable clinical outcome as assessed by the mRS score.

6.3.2.2 Change from Baseline in mRS Scores in Patients with Ruptured Aneurysms

Baseline mRS scores were obtained for all patients, including those with a ruptured aneurysm (n=9). All patients were followed with mRS scores through 12 months. The analysis of change in mRS score in patients with ruptured aneurysms utilized a worst-case approximation for the 1 patient with a missing mRS score at 12 months. This patient was evaluated as mRS 1 at baseline, discharge, and 30-day follow-up; therefore, the mRS at follow-up was carried forward for this patient.

After treatment with the WEB, 7 out of the 9 patients with ruptured aneurysms (77.78%) demonstrated an unchanged mRS score at 12 months (Table 25). Two patients with baseline ruptured aneurysms had an mRS improvement of 1 point (to mRS 0) from baseline to 12 months. More than half of the treated ruptured aneurysms were located in the posterior cerebral circulation (5/9, 56% basilar apex). Posterior circulation WNBAs, especially those at the basilar tip, are especially difficult to treat and have high surgical mortality and morbidity (Wiebers et al. 2003). Yet in the WEB-IT Study, none of the ruptured aneurysm patients were noted to worsen based upon mRS score despite using the worst-case approximation technique, and 2 improved. These findings support the use of WEB in ruptured aneurysms.

Table 25: mRS Change from Baseline to 12 Months in Ruptured Aneurysms in WEB-IT

mRS Score at Baseline	mRS Score at 12-Months		Total
	0 n (%)	1 n (%)	
0	5 (100.00)	0 (0.00)	5
1	2 (50.00)	2 (50.00)	4
Total	7 (77.78)	2 (22.22)	9

6.4 Overview of Adverse Events

A total of 348 AEs occurred in the 150 patients enrolled in WEB-IT through 12 months. Of the overall AEs, 286 were non-serious AEs occurring in 104 patients, and 62 were SAEs occurring in 33 patients. No deaths have occurred in the study through the 12-month primary endpoint follow-up period.

6.5 Common Adverse Events

Within the first 30 days post-treatment (ie, peri-procedural), 135 non-serious AEs occurred in 68 patients (45.3%). Of the 135 non-serious AEs, the most common peri-procedural non-serious AEs were:

- Headache (20 events/20 patients, 13.3%)
- Nausea (10 events/9 patients, 6.0%)
- Vessel puncture site related events (13 events including puncture site reaction, bruise, hematoma, hemorrhage, and pain)

No other non-serious AEs occurred within the first 30 days of treatment in greater than 5% of patients.

Between day 31 and 12 months, 151 non-serious events occurred in 65 patients. The most common event occurring between day 31 and 12 months was headache (24 events in 20 patients, 13.3%). No other non-serious event occurred in more than 5% of patients.

A listing of all common AEs occurring in ≥ 2 patients can be found in Appendix 11.4.

6.6 Serious Adverse Events

6.6.1 Overview of Serious Adverse Events

Serious AEs are summarized in Table 26. A total of 62 SAEs occurred in 33 patients (22%) through 12 months. Within the first 30 days after WEB implantation, 21 patients (14.0%) experienced 27 SAEs. The most common events in this period were ischemic stroke (6), vessel puncture site hematoma (3), SAH (2), and TIA (2).

Between day 31 and 12 months, 21 patients (14.0%) experienced 35 SAEs. These events were distributed across the system organ classes and were generally associated with the age and baseline comorbidities of the population treated. Nervous system disorders accounted for 8 of the 35 events and included intracranial hemorrhage, ischemic stroke, headache, TIA, seizure, and benign intracranial hypertension.

Table 26: Serious Adverse Events (> 1 Patient) within 12 months in WEB-IT

System Organ Class	Preferred Term	SAE Rate[a] n (%) N=150	Number of Events
Serious Adverse Events within 30 Days			
All	Any	21 (14.00)	27
General disorders and administration site conditions	Vessel puncture site haematoma	3 (2.00)	3
Nervous system disorders	Ischaemic Stroke	6 (4.00)	6
	Subarachnoid haemorrhage	2 (1.33)	2
	Transient ischaemic attack	2 (1.33)	2
Serious Adverse Events from Day 31 to 12 Months			
All	All	21 (14.00)	35
Gastrointestinal disorders	Gastrointestinal haemorrhage	2 (1.33)	2
Nervous system disorders	Transient ischaemic attack	2 (1.33)	3

[a]Summing across preferred terms or system organ classes may not result in the same sum overall because of multiple events per patient even in the same preferred term or organ class.

6.6.2 Procedure- and Device-Related Serious Adverse Events

Procedure- and device-related SAEs are summarized in Table 27. There was 1 SAE (SAH during procedure) within 30 days of the procedure considered to be related to the device and use of an ancillary device (microcatheter).

There were 11 procedure-related SAEs: 3 ischemic strokes, 3 vessel puncture site hematomas, and 1 event each of TIA, SAH, aphasia, confusional state, and vomiting. These serious procedure-related events are expected in both nature and frequency with the treatment of aneurysms.

There were 3 SAEs in 3 patients within 30 days of the procedure that were related to both the procedure and the device.

- There was a TIA on day 8 in 1 patient. This event was considered serious because it required hospitalization.
- One event was related to branch or parent arterial thrombosis near the WEB device that occurred during the procedure and was treated with placement of a Neuroform stent.
- One minor ischemic stroke on day 10 required hospitalization; the patient's 7-day NIHSS was 0.

Table 27: Procedure- and Device-Related Serious Adverse Events in WEB-IT

System Organ Class	Preferred Term	Event Rate n (%) N=150	Number of Events[b]
Procedure-Related SAEs			
All	All	10 (6.67)	11
Gastrointestinal disorders	Vomiting	1 (0.67)	1
General disorders and administration site conditions	Vessel puncture site haematoma	3 (2.00)	3
Nervous system disorders	Aphasia	1 (0.67)	1
	Ischaemic Stroke	3 (2.00)	3
	Subarachnoid haemorrhage	1 (0.67)	1
	Transient ischaemic attack	1 (0.67)	1
Psychiatric disorders	Confusional state	1 (0.67)	1
Device-Related SAEs			
SAE within 30 Days[a]			
All	All	1 (0.67)	1
Nervous system disorders	Subarachnoid haemorrhage	1 (0.67)	1
Joint Device- and Procedure-Related SAEs			
SAE within 30 Days[a]			
All	All	3 (2.00)	3
Nervous system disorders	Ischaemic Stroke	1 (0.67)	1
	Transient ischaemic attack	1 (0.67)	1
Vascular disorders	Arterial thrombosis	1 (0.67)	1

[a]There were no device-related SAE beyond 30 days
[b]One patient experienced 2 SAEs

6.7 Adverse Events by Aneurysm Location and Size

As shown in Table 28, there was no statistically significant difference in the rate of AEs by aneurysm location. There was a trend toward more events at the basilar location; however, further examination of neurological events (Table 29) showed no significant difference in the rate of these AEs by aneurysm location, which suggests that the trend was a chance finding associated with non-neurological events and not related to anatomic location.

Table 28: Adverse Events by Anatomic Location in WEB-IT

Aneurysm Location	Patients with at Least One Event n (%)	N	Number of Events
AComm	26 (65.00)	40	98
Basilar	46 (77.97)	59	163
ICA	3 (50.00)	6	6
MCA	25 (55.56)	45	81

Table 29: Neurological Adverse Events by Anatomic Location in WEB-IT

Aneurysm Location	Patients with at Least One Event n (%)	N	Number of Events
AComm	7 (17.50)	40	11
Basilar	6 (10.17)	59	9
ICA	2 (33.33)	6	2
MCA	8 (17.78)	45	11

Note: Neurological AEs include aphasia, TIA, ischemic stroke, SAH, intracranial hemorrhage, vasospasm, seizure

Additional analyses showed no statistically significant difference in the total rate of AEs by aneurysm diameter (Table 30). Similarly, further examination of neurological events showed no significant difference in the rate of AEs by aneurysm diameter (Table 31).

Table 30: Total Adverse Events by Size Category in WEB-IT

Size (Aneurysm Diameter, mm)	Patients with at Least One Event n (%)	N	Number of Events
≤ 5.0	22 (59.5)	37	65
5.1-7.99	59 (67.1)	88	235
≥ 8.0	19 (76.0)	25	48

Table 31: Neurological Adverse Events by Size Category in WEB-IT

Size (Aneurysm Diameter, mm)	Patients with at Least One Event n (%)	N	Number of Events
≤ 5.0	6 (16.2)	37	6
5.1-7.99	14 (15.9)	88	21
≥ 8.0	3 (12.0)	25	6

Note: Neurological AEs include aphasia, TIA, ischemic stroke, SAH, intracranial hemorrhage, vasospasm, and seizure

6.8 Adverse Events of Special Interest

6.8.1 Overview of Adverse Events of Special Interest

Adverse Events of Special Interest included thromboembolic events, TIA, ischemic strokes, SAH, intracranial hemorrhage, vasospasm, seizure, perforation or rupture of the parent or branch arteries, stenosis of the parent or branch arteries, thrombosis of the parent or branch (perforator) arteries, bleeding events of gastrointestinal hemorrhage, hemoptysis, epistaxis, or other events adjudicated as strokes (1 aphasia event).

Table 32 provides a summary of all AESIs that occurred in WEB-IT through 12 months. There were 37 events classified as AESIs that occurred in 28 patients (18.7%). Details on strokes and SAH can be found in Sections 6.8.2 and 6.8.2.1, respectively.

Table 32: Adverse Events of Special Interest within 12 months in WEB-IT

Preferred Term	Patients n (%) N=150	Events n (%) N=348
Aphasia	1 (0.67)	1 (0.29)
Embolism (Thromboembolic Event)	0 (0.00)	0 (0.00)
Transient Ischemic Attack (TIA)	6 (4.00)	10 (2.87)
Ischemic Stroke	9 (6.00)	10 (2.87)
SAH	3 (2.00)	3 (0.86)
Intracranial Hemorrhage	1 (0.67)	1 (0.29)
Vasospasm	5 (3.33)	5 (1.43)
Seizure	2 (1.33)	2 (0.57)
Perforation/Rupture of parent or branch artery	0 (0.00)	0 (0.00)
Stenosis – Parent or branch artery	0 (0.00)	0 (0.00)
Thrombosis – Parent or branch artery	3 (2.00)	3 (0.86)
Gastrointestinal Haemorrhage (GI Bleed)	2 (1.33)	2 (0.57)
Hemoptysis	0 (0.00)	0 (0.00)
Epistaxis	0 (0.00)	0 (0.00)

6.8.2 All Strokes

Based on the protocol definition of stroke (a new neurologic deficit of presumed vascular origin, persisting more than 24 hours in the absence of a neuroimaging study clearly indicating a different etiology), 10 patients experienced a total of 11 ischemic stroke events (6.0%): 10 minor ischemic strokes and 1 transient post-procedural aphasia conservatively counted as an ischemic stroke. Of these 11 events, 8 resolved without sequelae and 3 resulted in minor sequelae with mRS scores of 1 at 12 months.

There were 4 hemorrhagic stroke events: 1 SAH (the primary safety event, discussed in Section 6.2), 2 procedural SAHs, and 1 intracranial hemorrhage. The procedural SAH events were identified by contrast extravasation around the index aneurysm. In 1 patient, contrast extravasation was noted intra-procedurally, and in the other patient, contrast extravasation was noted on a routine CT on the day after the procedure. Both events were asymptomatic, resolved without sequelae, and considered to be device-related. The patient with intracranial hemorrhage presented on day 139 with a

headache, and the event resolved without sequelae or change in mRS score. This event was considered unrelated to device or procedure.

More details can be found in Table 33.

Table 33: Detailed Information on Stroke Events in WEB-IT

Patient	MedDRA Preferred Term	Major/ Minor	NIHSS at study entry	NIHSS at event ictus	NIHSS at day 7 after event	12 Month mRS	Event Timing	Relatedness	Location
Ischemic									
1	Ischemic stroke	Minor	0	NA	1	0	93	Concurrent condition or treatment	Ipsilateral
2	Ischemic stroke	Minor	0	0	0	0	218	Related to the study disease condition, Concurrent condition or treatment	Contralateral
3	Ischemic stroke	Minor	0	1	0	1	8	Procedure	Contralateral
4	Ischemic stroke	Minor	0	4	0	4	1	Procedure	Ipsilateral
5	Ischemic stroke	Minor	2	4	2	1	1	Procedure	Ipsilateral
6	Ischemic stroke	Minor	0	0	0	1	10	Device, Procedure	Ipsilateral
7	Ischemic stroke	Minor	0	1	1	1	12	Concurrent condition or treatment	Contralateral
	Ischemic stroke	Minor		3	2		72	Concurrent condition or treatment	Contralateral
8	Ischemic stroke	Minor	1	0	0	NA	24	Concurrent condition/treatment	Contralateral
9	Ischemic stroke	Minor	0	2	1	1	27	Concurrent condition or treatment	Ipsilateral
10	Aphasia	Minor	0	10	0	0	0	Procedure	Ipsilateral
Hemorrhagic									
4	Subarachnoid hemorrhage	Major	0	14	13	4	22	Procedure, Concurrent condition or treatment	Ipsilateral
11	Subarachnoid hemorrhage	Minor	0	0	0	0	0	Device, use of an ancillary device	Ipsilateral
12	Subarachnoid hemorrhage	Minor	0	NA	NA	0	1	Device, use of an ancillary device	N/A
13	Intracranial hemorrhage	Minor	0	NA	NA	0	139	Unrelated	N/A

*This patient had an ischemic stroke on day 1 and an SAH in the same territory on day 22

6.8.2.1 FDA-Requested All Stroke Post-hoc Analysis

At the request of the FDA, a post-hoc analysis was also conducted that incorporated all strokes observed during the 1-year follow-up as a worst-case assessment. In this analysis, the protocol definition for the primary safety endpoint was applied with replacement of the word *major* with *any*:

> The proportion of patients with death of any nonaccidental cause or any stroke (ischemic or hemorrhagic) within the first 30 days after treatment or any ipsilateral stroke or death due to neurologic cause from day 31 to 12 months after treatment. For this analysis a patient would be considered a safety failure upon meeting any of these criteria.

Table 34 shows the 12 patients[3] adjudicated to have at least 1 stroke event of any severity over the 12 months consistent with the definition above. Of these 12 strokes, 5 were considered to be unrelated to either device or procedure, and 3 of the strokes within 30 days were located on the contralateral side of the brain from the treated aneurysm. In this analysis, the all stroke rate in WEB-IT was 8.0%, and even the upper two-sided 95% confidence limit of 13.56% was well below the PG of 20%.

Table 34: FDA-Requested All Stroke Post-hoc Analysis in WEB-IT

Endpoint	Rate	95% Confidence Interval
Composite FDA-requested All Stroke Safety endpoint	12[a]/150 (8.00%)[b]	(4.20,13.56)
Death within 30 days	0/150 (0.00%)	(0.00, 2.43)
Any Stroke within 30 days	10/150 (6.67%)	(3.24, 11.92)
Any Ipsilateral Stroke Day 31 to 12 Months	2/147 (1.36%)	(0.17, 4.83)
Neurological Death Day 31 to 12 Months	0/147 (0.00)	(0.00, 2.48)

[a] One patient experienced two events, (SAH and Ischemic Stroke)
[b] Patients include: hemorrhagic stroke (4), SAH (1), intracranial hemorrhage (1), ischemic stroke (8), and aphasia (1)

[3] When compared to Table 33, 3 patients were excluded for not meeting the post-hoc definition of stroke.

7 GLOBAL EXPERIENCE

7.1 Global WEB Approvals

The WEB received CE mark in the European Union in 2010 and is approved in 44 countries. The WEB has not been withdrawn from the market for any reason. To date, more than 6,000 WEB devices have been implanted globally.

In 2017, Reportable Events occurred in 0.09% (3/3283) devices sold. All 3 events were procedural ruptures; 2 events were associated with inadvertent advancement of the microcatheter, and 1 occurred during manipulation of the WEB within the aneurysm.

7.2 Completed Post-Market Studies Conducted Using GCP Guidelines

Four post-market studies, WEBCAST, WEBCAST-2, French Observatory, and CLARYS, have been conducted using GCP guidelines since the introduction of the WEB device in Europe in 2010.

The WEBCAST, WEBCAST-2, and French Observatory studies were single-arm, prospective, post-market consecutive, multicenter studies dedicated to the evaluation of WEB treatment for bifurcation aneurysms (Table 35). The cumulative population included 168 patients with 169 aneurysms; 51% of the aneurysms were located in the MCA, and 18% were located in the basilar artery. CLARYS is a single-arm, prospective, post-market, multicenter study assessing the clinical utility of the WEB in ruptured aneurysms that has follow-up through 30 days but has no patient follow-up through 12 months (CLARYS data was not presented to the Agency in the PreMarket Approval application).

Table 35: Completed WEB Post-Market Studies Conducted Using GCP Guidelines

	WEBCAST	French Observatory	WEBCAST-2	CLARYS
Study Type	Single-arm, prospective, post-market, multicenter, GCP	Single-arm, prospective, post-market, multicenter, GCP	Single-arm, prospective, post-market, multicenter, GCP	Single-arm, prospective, post-market, multicenter, GCP
N Patients (N aneurysms)	51 (51)	62 (63)	55 (55)	60 (66)
Aneurysm Population Treated	Intracranial wide-neck (≥ 4mm) aneurysms deemed appropriate for endovascular treatment in the BA, MCA bifurcation, ICAt, and AComm	Intracranial wide-neck (Dome to neck ratio ≥ 1) aneurysms deemed appropriate for endovascular treatment in the BA, MCA bifurcation, ICAt, and ACA	Intracranial wide-neck (Dome to neck ratio ≥ 1) aneurysms deemed appropriate for endovascular treatment in the BA, MCA bifurcation, ICAt, and ACA	Single IAs ruptured within 30 days requiring treatment according to a multidisciplinary decision. Aneurysms must be saccular and be located in the BA, MCA bifurcation, ICAt, AComm, ACA, or PComm.

Completed Follow-up Evaluations	30 days, 3 months (optional), 6 months, 12 months, 24 months	30 days, 12 months, 24 months	30 days, 12 months, 24 months	30 days
30 Day Morbidity and Mortality Summary	• No mortality at 30 days. • One patient (1.96%) with a ruptured aneurysm had morbidity at 30 days (mRS 3) related to initial SAH (Hunt & Hess 3) and was mRS 1 at 6 months. • One patient treated for an unruptured aneurysm was mRS 2 preoperatively due to a previous SAH (from another aneurysm) and remained mRS 2 at 30 days. • Morbidity related to the treatment was 0.0%.	• No mortality at 30 days. • Two patients (3.2%) had morbidity at 30 days (1 patient had mRS 2 at baseline and mRS 3 at 30 days due to mass effect, 1 patient with a ruptured aneurysm at baseline had mRS 3 at 30 days). • Morbidity related to the treatment was 0.0%.	• No mortality at 30 days. • Procedural morbidity was observed in 1/55 patients (1.8%) related to a thromboembolic event (mRS 3). • One patient (1.8%) with a ruptured aneurysm was mRS 4 at 30 days due to the initial bleeding.	• One death occurred within 30 days; the patient experienced a vasospasm and died 6 days post-procedure. The event was adjudicated as related to the study disease condition. • Morbidity (mRS > 2 if pre-rupture ≤ 2 or mRS +1 if pre-rupture mRS > 2) at 30 days was observed in 9/60 patients (15.0%).
Effectiveness Results Summary	• Adequate occlusion (complete or neck remnant) at 12 months was exhibited in 36/42 aneurysms (85.7%). • Complete occlusion at 12 months was exhibited in 26/42 aneurysms (61.9%).	• Adequate occlusion (complete or neck remnant) at 12 months was exhibited in 46/58 aneurysms (79.3%). • Complete occlusion at 12 months was exhibited in 30/58 aneurysms (51.7%).	• Adequate occlusion (complete or neck remnant) at 12 months was exhibited in 40/50 aneurysms (80.0%). • Complete occlusion at 12 months was exhibited in 27/50 aneurysms (54.0%).	• The re-bleeding rate reported up to 1-month was 0.0%. • There were 3 intraprocedural neurological events with clinical impact; none were related to the device.

BA=Basilar Artery, MCA=Middle Cerebral Artery, ICAt=Internal Carotid Artery terminus, AComm=Anterior Communicating Artery, ACA=Anterior Cerebral Artery, PComm=Posterior Communicating Artery.

Overall in WEBCAST, French Observatory, and WEBCAST-2, treatment was successfully performed in 163/169 aneurysms (96.4%). A collective intraprocedural rupture rate of 1.2% (2/167 cases) with no (0%) associated disability or perioperative mortality was reported. There was no mortality at 1 month, and global morbidity was observed in 5/167 patients (3.0%). All-cause, neuro-related, and procedure-related mortality at 12 months were 5/153 (3.3%), 1/153 (0.7%), and 1/153 (0.7%), respectively.

At 12 months, complete occlusion was seen in 81/153 aneurysms (52.9%), neck remnant in 40/153 aneurysms (26.1%), and aneurysm remnant in 32/153 aneurysms (20.9%). Adequate occlusion

(Complete Occlusion or Neck Remnant) was observed in 121/153 aneurysms (79.1%). Twenty-five of the WEBCAST study patients have 3-year follow-up data that suggest durability of the 12 months complete occlusion results.

Additionally, there have been no (0%) late or delayed rupture or re-bleeding of the index aneurysm in any of the patient cohorts in the 3 studies with 1-4 years of follow-up to date. There have also been no (0%) postprocedural ruptures or re-ruptures reported.

7.3 Ongoing Post-Market Study Conducted Using GCP Guidelines

WEB-IT China is an ongoing single-arm, prospective, multicenter pre-market study that has begun enrollment of patients with ruptured or unruptured IAs in China. Study details are summarized in Table 36.

Table 36: Ongoing Post-Market Study Conducted Using GCP Guidelines – WEB-IT China

Study Type	Single-arm, prospective, pre- market, multicenter, GCP
No. of Patients Enrolled	43 patients enrolled as of August 19, 2018.
Target Aneurysm Population	Single ruptured or unruptured IA requiring treatment. If the patient has an additional IA requiring treatment, the additional IA must not require treatment within 60 days of the index procedure. Aneurysms must have dome-to-neck ratio ≥ 1 and be wide neck (≥ 4mm neck or dome-to-neck ratio < 2). Aneurysms must be saccular and be located in the BA, MCA bifurcation, ICAt, or AComm.
Planned Follow-up Evaluations per Protocol	30 days, 6 months, 12 months

BA=Basilar Artery, MCA=Middle Cerebral Artery, ICAt=Internal Carotid Artery terminus, AComm=Anterior Communicating Artery, ACA=Anterior Cerebral Artery

8 POST-MARKET PLAN

8.1 Study Follow-Up

Data will continue to be collected for the 150 patients in WEB-IT through the 5-year follow-up period (Table 37). Follow-up visits for WEBCAST and WEBCAST-2 will also be conducted for up to 5 years. Total enrollment in these studies is 263 patients.

Table 37: Planned WEB Study Follow-Up

GCP Study	Sample Size	Duration (Years)	Rupture Status
WEB-IT	150	5	Ruptured or Unruptured
WEBCAST	51	5	Ruptured Unruptured
WEBCAST-2	55	5	
French Observatory	62	2	
CLARYS	60	1	Ruptured

8.2 Physician and Specialist Training

A Centralized New User WEB Training Program has been established by the sponsor to ensure physicians have adequate experience with the WEB and associated system. The centralized training course provides physicians with in-depth didactic and hands-on training for the WEB. The course content includes:

- a technical overview of the device and implantation procedure
- case preparation and planning
- proper device sizing and selection
- orientation to the occlusion scale
- review of the safety and effectiveness clinical data
- case examples
- hands-on training with a replicator.

Physicians must complete a minimum of 3 proctor-supported cases and 5 additional cases as the primary operator prior to using the WEB in clinical practice.

9 BENEFIT/RISK ANALYSIS

The WEB is a novel, first-of-a-kind device for treating WNBAs, overcoming anatomical challenges associated with these difficult-to-treat cerebral aneurysms. The WEB brings patients with this life-threatening condition a new option with improved effectiveness and a low rate of complications.

The Sponsor has presented valid scientific evidence from a well-designed clinical study demonstrating that the WEB is both a safe and effective treatment option for patients with WNBAs, and that the benefits of the device outweigh the potential risks.

9.1 Observed Benefits

The WEB led to successful aneurysm occlusion in 54.8% of patients in WEB-IT. The following benefits were observed in the study:

- WEB-IT met the primary effectiveness success criteria ($p < 0.0001$)
    - The success rate, defined as the proportion of patients with complete aneurysm occlusion without retreatment, without recurrent SAH, and without clinically significant (> 50%) parent artery stenosis at 12 months after treatment, was 54.8% in the ITT Population (lower bound of one-sided 95% CI of 48.0%).
    - 53.9% of patients achieved complete aneurysm occlusion at 12-month follow-up, and 86.2% achieved adequate occlusion (Complete Occlusion or Neck Remnant) in CC population.
    - In patients with complete occlusion, there were no patients with parent artery stenosis > 50%.
    - 5.6% of patients underwent or had planned target aneurysm retreatment through 378 days.
    - There were no recurrent SAH events or late ruptures during the study among the patients presenting with ruptured aneurysms at baseline.
- There were no differences in the proportion of patients meeting the effectiveness success criteria by aneurysm location or aneurysm size.
- There were no deaths, major ipsilateral strokes from day 31 to 12 months, neurological deaths, or unanticipated adverse device effects.

9.2 Possible Risks

- WEB-IT met the primary safety success criteria ($p < 0.0001$).
    - 1 patient (0.67%) had a primary safety event.
- Within the first 30 days after WEB implantation, 21 patients experienced 27 SAEs. These events mostly fell into the category of nervous system disorders and included events of ischemic stroke, vessel puncture site hematoma, SAH, and TIA.

- Between day 31 and 12 months, 21 patients experienced 35 SAEs. These events were distributed across the system organ classes.
- 6.7% of AEs were attributed to the device.
    - These AEs were primarily non-serious and resolved without sequelae in nearly all cases.
- There were 15 stroke events in 13 patients: 11 were minor ischemic strokes, 2 were asymptomatic procedural ruptures, 1 was a major SAH (primary safety event), and 1 was a minor intracranial hemorrhage.

9.3 Overall Benefit/Risk Profile

When comparing the benefit/risk profile for the WEB device to alternative treatment modalities, treatment with the WEB remains favorable. Table 38 shows a comparison of occlusion rates, and morbidity and mortality with coiling and stent-assisted coiling (Hetts et al. 2014) with results from both the pivotal WEB-IT study and data from WEBCAST, WEBCAST-2, and French Observatory.

The WEB-IT effectiveness data for complete occlusion are similar to or better than treatment with primary coiling or stent-assisted coiling. The benefit/risk profile of WEB is further bolstered by its safety profile (morbidity and mortality) and retreatment rates, which are similar to or better than currently available devices.

Table 38: Key Comparative Results of WEB with Coiling and Stent-Assisted Coiling

Treatment	Study	Complete Occlusion	Morbidity and Mortality
Coiling	MAPS/Hetts – AJNR 2014 – Wide Neck Aneurysms	27.1% (12 months)	1.5% (12 months)
Stent-Assisted Coiling	MAPS/Hetts – AJNR 2014 – Wide Neck Aneurysms	45.7% (12 months)	7.5% (12 months)
Endovascular Techniques	BRANCH/De Leacy – JNIS 2018 – WNBAs	30.6% (12 months)	5.8% morbidity, 1.7% mortality (12 months)
WEB	3 GCP Pierot – JNIS 2018 – WNBAs	52.9% (12 months)	3.0% (12 months)
WEB	WEB-IT – WNBA	54.8% (12 months)	1.3% (12 months)

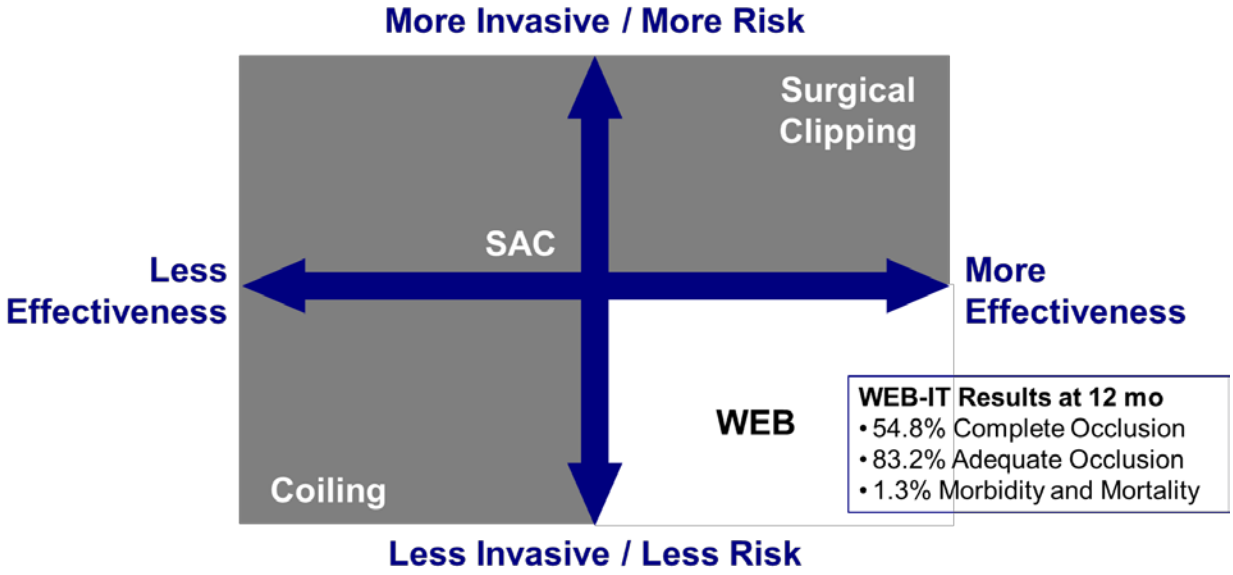
[a] Coiling WNA cohort n=73 in retreatment analysis and n=59 in 12-month occlusion analysis
[b] SAC WNA cohort n=85 in retreatment analysis and n=70 in 12-month occlusion analysis

9.4 Conclusion

Patients with WNBAs are at increased risk of sudden and potentially fatal bleeding. Few options are available to safely and effectively treat the specific size, shape, and location of WNBAs.

In terms of both complete and adequate occlusion, the WEB offers more benefit than current endovascular treatments for WNBAs, with fewer recurrences. Figure 17 qualitatively depicts the benefit/risk profile of the WEB compared to these alternatives. The WEB rebalances the benefit/risk equation for patients and physicians when considering an appropriate treatment for WNBAs.

Figure 17: Benefit/Risk Assessment of the WEB



10 REFERENCES

Adeeb, N., C. J. Griessenauer, A. S. Patel, P. M. Foreman, C. E. Baccin, J. M. Moore, R. Gupta, A. Alturki, M. R. Harrigan, C. S. Ogilvy and A. J. Thomas (2018). "The Use of Single Stent-Assisted Coiling in Treatment of Bifurcation Aneurysms: A Multicenter Cohort Study With Proposal of a Scoring System to Predict Complete Occlusion." Neurosurgery **82**(5): 710-718.

Andaluz, N. and M. Zuccarello (2008). "Anterior Communicating Artery Aneurysm Surgery through the Orbitopterional Approach: Long-Term Follow-Up in a Series of 75 Consecutive Patients." Skull Base **18**(4): 265-274.

Backes, D., M. D. Vergouwen, B. K. Velthuis, I. C. van der Schaaf, A. S. Bor, A. Algra and G. J. Rinkel (2014). "Difference in aneurysm characteristics between ruptured and unruptured aneurysms in patients with multiple intracranial aneurysms." Stroke **45**(5): 1299-1303.

Bartolini, B., R. Blanc, S. Pistocchi, H. Redjem and M. Piotin (2014). ""Y" and "X" stent-assisted coiling of complex and wide-neck intracranial bifurcation aneurysms." AJNR Am J Neuroradiol **35**(11): 2153-2158.

Bendok, B. (2018). New Generation Hydrogel Endovascular Aneurysm Treatment Trial (HEAT). Annual Conference of the Society of NeuroInterventional Surgery. San Francisco, CA.

Birknes, J. K., S. K. Hwang, A. S. Pandey, K. Cockroft, A. M. Dyer, R. P. Benitez, E. Veznedaroglu and R. H. Rosenwasser (2006). "Feasibility and limitations of endovascular coil embolization of anterior communicating artery aneurysms: morphological considerations." Neurosurgery **59**(1): 43-52; discussion 43-52.

Brisman, J. L., J. K. Song and D. W. Newell (2006). "Cerebral aneurysms." N Engl J Med **355**(9): 928-939.

Castano, C., M. Terceno, S. Remollo, M. R. Garcia-Sort and C. Dominguez (2017). "Endovascular treatment of wide-neck intracranial bifurcation aneurysms with 'Y'-configuration, double Neuroform(R) stents-assisted coiling technique: Experience in a single center." Interv Neuroradiol **23**(4): 362-370.

Chalouhi, N., P. Jabbour, L. F. Gonzalez, A. S. Dumont, R. Rosenwasser, R. M. Starke, D. Gordon, S. Hann and S. Tjoumakaris (2012). "Safety and efficacy of endovascular treatment of basilar tip aneurysms by coiling with and without stent assistance: a review of 235 cases." Neurosurgery **71**(4): 785-794.

De Leacy, R. A., K. M. Fargen, J. R. Mascitelli, J. Fifi, L. Turkheimer, X. Zhang, A. B. Patel, M. J. Koch, A. S. Pandey, D. A. Wilkinson, J. Griauzde, R. F. James, E. M. Fortuny, A. Cruz, A. Boulos, E. Nourollah-Zadeh, A. Paul, E. Sauvageau, R. Hanel, P. Aguilar-Salinas, R. L. Novakovic, B. G. Welch, R. Almardawi, G. Jindal, H. Shownkeen, E. I. Levy, A. H. Siddiqui and J. Mocco (2018). "Wide-neck bifurcation aneurysms of the middle cerebral artery and basilar apex treated by endovascular techniques: a multicentre, core lab adjudicated study evaluating safety and durability of occlusion (BRANCH)." J Neurointerv Surg.

Fargen, K. M., J. Mocco, D. Neal, M. C. Dewan, J. Reavey-Cantwell, H. H. Woo, D. J. Fiorella, M. Mokin, A. H. Siddiqui, A. S. Turk, R. D. Turner, I. Chaudry, M. Y. Kalani, F. Albuquerque and B. L. Hoh (2013). "A multicenter study of stent-assisted coiling of cerebral aneurysms with a Y configuration." Neurosurgery **73**(3): 466-472.

Fiorella, D., A. Arthur, J. Byrne, L. Pierot, A. Molyneux, G. Duckwiler, T. McCarthy and C. Strother (2015). "Interobserver variability in the assessment of aneurysm occlusion with the WEB aneurysm embolization system." J Neurointerv Surg **7**(8): 591-595.

Fiorella, D., A. S. Arthur, R. Chiacchierini, E. Emery, A. Molyneux and L. Pierot (2017). "How safe and effective are existing treatments for wide-necked bifurcation aneurysms? Literature-based objective performance criteria for safety and effectiveness." J Neurointerv Surg **9**(12): 1197-1201.

Food and Drug Administration (2018). "Brief Summary of the Neurological Devices Panel of the Medical Devices Advisory Committee Meeting on March 1, 2018."

Gao, B., M. I. Baharoglu, A. D. Cohen and A. M. Malek (2013). "Y-stent coiling of basilar bifurcation aneurysms induces a dynamic angular vascular remodeling with alteration of the apical wall shear stress pattern." Neurosurgery **72**(4): 617-629; discussion 628-619.

Guo, X. B., B. J. Yan and S. Guan (2014). "Waffle-cone technique using solitaire AB stent for endovascular treatment of complex and wide-necked bifurcation cerebral aneurysms." J Neuroimaging **24**(6): 599-602.

Hetts, S. W., A. Turk, J. D. English, C. F. Dowd, J. Mocco, C. Prestigiacomo, G. Nesbit, S. G. Ge, J. N. Jin, K. Carroll, Y. Murayama, A. Gholkar, S. Barnwell, D. Lopes, S. C. Johnston, C. McDougall, Matrix and I. Platinum Science Trial (2014). "Stent-assisted coiling versus coiling alone in unruptured intracranial aneurysms in the matrix and platinum science trial: safety, efficacy, and mid-term outcomes." AJNR Am J Neuroradiol **35**(4): 698-705.

Hop, J. W., G. J. Rinkel, A. Algra and J. van Gijn (1997). "Case-fatality rates and functional outcome after subarachnoid hemorrhage: a systematic review." Stroke **28**(3): 660-664.

Huang, J. and J. M. van Gelder (2002). "The probability of sudden death from rupture of intracranial aneurysms: a meta-analysis." Neurosurgery **51**(5): 1101-1105; discussion 1105-1107.

Ko, J. K., I. H. Han, W. H. Cho, B. K. Choi, S. H. Cha, C. H. Choi, S. W. Lee and T. H. Lee (2015). "Crossing Y-stent technique with dual open-cell stents for coiling of wide-necked bifurcation aneurysms." Clin Neurol Neurosurg **132**: 54-60.

Lee, K., H. Park, I. Park, S. Q. Park, O. K. Kwon and J. Han (2016). "Y-configuration Stent-assisted Coil Embolization for Wide-necked Intracranial Bifurcation Aneurysms." J Cerebrovasc Endovasc Neurosurg **18**(4): 355-362.

Limbucci, N., L. Renieri, S. Nappini, A. Consoli, A. Rosi and S. Mangiafico (2016). "Y-stent assisted coiling of bifurcation aneurysms with Enterprise stent: long-term follow-up." J Neurointerv Surg **8**(2): 158-162.

Lubicz, B., J. Klisch, J. Y. Gauvrit, I. Szikora, M. Leonardi, T. Liebig, N. P. Nuzzi, E. Boccardi, F. D. Paola, M. Holtmannspotter, W. Weber, E. Calgliari, V. Sychra, B. Mine and L. Pierot (2014). "WEB-DL endovascular treatment of wide-neck bifurcation aneurysms: short- and midterm results in a European study." AJNR Am J Neuroradiol **35**(3): 432-438.

Lusseveld, E., E. H. Brilstra, P. C. Nijssen, W. J. van Rooij, M. Sluzewski, C. A. Tulleken, D. Wijnalda, R. L. Schellens, Y. van der Graaf and G. J. Rinkel (2002). "Endovascular coiling versus neurosurgical clipping in patients with a ruptured basilar tip aneurysm." J Neurol Neurosurg Psychiatry **73**(5): 591-593.

McDougall, C. G., S. C. Johnston, A. Gholkar, S. L. Barnwell, J. C. Vazquez Suarez, J. Masso Romero, J. C. Chaloupka, A. Bonafe, A. K. Wakhloo, D. Tampieri, C. F. Dowd, A. J. Fox, S. J. Imm, K. Carroll, A. S. Turk and M. Investigators (2014). "Bioactive versus bare platinum coils in

the treatment of intracranial aneurysms: the MAPS (Matrix and Platinum Science) trial." AJNR Am J Neuroradiol **35**(5): 935-942.

Mitsos, A. P., M. D. Giannakopoulou, I. G. Kaklamanos, M. Kapritsou, M. I. Konstantinou, T. Fotis, K. V. Mamoura, T. Mariolis-Sapsakos, I. T. Ntountas and E. A. Konstantinou (2013). "Endovascular treatment of cerebral aneurysms in relation to their parent artery wall: a single center study." Neuroradiol J **26**(1): 71-79.

Murayama, Y., H. Arakawa, T. Ishibashi, D. Kawamura, M. Ebara, K. Irie, H. Takao, S. Ikeuchi, T. Ogawa, M. Kato, I. Kajiwara, S. Nishimura and T. Abe (2013). "Combined surgical and endovascular treatment of complex cerebrovascular diseases in the hybrid operating room." J Neurointerv Surg **5**(5): 489-493.

Naggara, O. N., P. M. White, F. Guilbert, D. Roy, A. Weill and J. Raymond (2010). "Endovascular treatment of intracranial unruptured aneurysms: systematic review and meta-analysis of the literature on safety and efficacy." Radiology **256**(3): 887-897.

Ogilvy, C. S. and B. S. Carter (2003). "Stratification of outcome for surgically treated unruptured intracranial aneurysms." Neurosurgery **52**(1): 82-87; discussion 87-88.

Pierot, L., J. Moret, X. Barreau, I. Szikora, D. Herbreteau, F. Turjman, M. Holtmannspotter, A. C. Januel, V. Costalat, J. Fiehler, J. Klisch, J. Y. Gauvrit, W. Weber, H. Desal, S. Velasco, T. Liebig, L. Stockx, J. Berkefeld, A. Molyneux, J. Byrne and L. Spelle (2018). "Safety and efficacy of aneurysm treatment with WEB in the cumulative population of three prospective, multicenter series." J Neurointerv Surg **10**(6): 553-559.

Pipeline Embolization Device Instructions for Use (2011).

Qui, T. and H. Xing (2014). "Morphological Distinguish of Rupture Status between Sidewall and Bifurcation Aneurysms." Int J Morphol **32**: 1111-1119.

Rankin, J. (1957). "Cerebral vascular accidents in patients over the age of 60. II. Prognosis." Scott Med J **2**(5): 200-215.

Rinkel, G. J., M. Djibuti, A. Algra and J. van Gijn (1998). "Prevalence and risk of rupture of intracranial aneurysms: a systematic review." Stroke **29**(1): 251-256.

Rodriguez-Hernandez, A., M. E. Sughrue, S. Akhavan, J. Habdank-Kolaczkowski and M. T. Lawton (2013). "Current management of middle cerebral artery aneurysms: surgical results with a "clip first" policy." Neurosurgery **72**(3): 415-427.

Rouchaud, A., W. Brinjikji, Y. H. Ding, D. Dai, Y. Q. Zhu, H. J. Cloft, D. F. Kallmes and R. Kadirvel (2016). "Evaluation of the Angiographic Grading Scale in Aneurysms Treated with the WEB Device in 80 Rabbits: Correlation with Histologic Evaluation." AJNR Am J Neuroradiol **37**(2): 324-329.

Roy, D., G. Milot and J. Raymond (2001). "Endovascular treatment of unruptured aneurysms." Stroke **32**(9): 1998-2004.

Sekhar, L. N., S. K. Natarajan, G. W. Britz and B. Ghodke (2007). "Microsurgical management of anterior communicating artery aneurysms." Neurosurgery **61**(5 Suppl 2): 273-290: discussion 290-272.

Suarez, J. I., R. W. Tarr and W. R. Selman (2006). "Aneurysmal subarachnoid hemorrhage." N Engl J Med **354**(4): 387-396.

Taschner, C. A., R. Chapot, V. Costalat, P. Machi, P. Courtheoux, X. Barreau, J. Berge, L. Pierot, K. Kadziolka, B. Jean, R. Blanc, A. Biondi, H. Brunel, S. Gallas, A. Berlis, D. Herbreteau, J.

Berkefeld, H. Urbach, S. Elsheikh, J. Fiehler, H. Desal, E. Graf and A. Bonafe (2018). "Second-Generation Hydrogel Coils for the Endovascular Treatment of Intracranial Aneurysms: A Randomized Controlled Trial." Stroke **49**(3): 667-674.

Vallee, J. N., A. Aymard, E. Vicaut, M. Reis and J. J. Merland (2003). "Endovascular treatment of basilar tip aneurysms with Guglielmi detachable coils: predictors of immediate and long-term results with multivariate analysis 6-year experience." Radiology **226**(3): 867-879.

Vlak, M. H., A. Algra, R. Brandenburg and G. J. Rinkel (2011). "Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis." Lancet Neurol **10**(7): 626-636.

Wiebers, D. O., J. P. Whisnant, J. Huston, 3rd, I. Meissner, R. D. Brown, Jr., D. G. Piepgras, G. S. Forbes, K. Thielen, D. Nichols, W. M. O'Fallon, J. Peacock, L. Jaeger, N. F. Kassell, G. L. Kongable-Beckman, J. C. Torner and I. International Study of Unruptured Intracranial Aneurysms (2003). "Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment." Lancet **362**(9378): 103-110.

11 APPENDICES

11.1 WEB Sizing

Table 39: Available WEB Sizes and Recommended Microcatheters

WEB SL/SLS EV Diameter (mm)	SL Heights Offered (mm)	SLS Height Offered (mm)	Minimum Microcatheter Inner Diameter (inches)	Recommended Microcatheter
4	3	2.6	0.021	VIA 21
	4			
5	3	3.6	0.021	
	4			
	5			
6	3	4.6	0.021	
	4			
	5			
7	3	5.6	0.021	
	4			
	5			
	6			
8	3	6.6	0.027	VIA 27
	4			
	5			
	6			
	7			
9	4	7.6	0.027	
	5			
	6			
	7			
	8			
10	5	8.6	0.032	VIA 33
	6			
	7			
	8			
11	6	9.6	0.03.2	
	7			
	8			
	9			

WEB SL EV = WEB Single Layer – Enhanced Visualization
WEB SLS EV = WEB Single Layer Sphere – Enhanced Visualization

11.2 Details on Core Laboratory, Clinical Events Adjudicator, and Data Monitoring Committee

Core Laboratory:

James Byrne, MD, FRCS, FRCR was the Core Laboratory reader for the WEB-IT Study, as well as for WEBCAST, French Observatory, and WEBCAST 2 studies. Professor Byrne and his Core Laboratory staff are affiliated with Oxford University Hospitals NHS Foundation Trust. He is a Consultant Interventional Neuroradiologist for Oxford University Hospitals and performed the first endovascular procedure using Guglielmi Detachable Coil (GDC) for aneurysm treatment in the UK in 1992.

Clinical Events Adjudicator:

Andrew Molyneux, MD was the CEA for the WEB-IT Study, as well as for the WEBCAST, French Observatory, and WEBCAST 2 Studies. Dr. Molyneux is a Sr. Clinical Research Fellow at the Nuffield Department of Surgery at the University of Oxford, UK, and is an honorary consultant neuroradiologist at the Oxford Radcliffe Hospitals NHS trust and the North Bristol NHS trust. He is credited with starting and finishing the seminal International Subarachnoid Aneurysm Trial (ISAT), which represents a landmark in the evolution in the treatment of cerebral aneurysms.

Data Monitoring Committee:

Alexander A. Khalessi, MD is a board-certified neurosurgeon who specializes in cranial and endovascular surgery. He is chair of the Department of Neurosurgery and director of endovascular neurosurgery. He provides both open surgical and catheter-based approaches to complex neurosurgical problems, including brain tumors, aneurysms, arteriovenous malformations (AVM) and carotid disease.

Glenn (Lee) Pride, MD is an Associate Professor of Radiology and Neurological Surgery and the Interventional Neuroradiology Program Director at UT Southwestern Medical Center. He specializes in the treatment of hemorrhagic and ischemic stroke, cerebral aneurysms, arteriovenous malformations, extra- and intracranial vascular occlusive lesions, facial vascular abnormalities, and spinal vascular abnormalities. He also serves as Director of the UT Southwestern fellowship programs in radiology and neuroradiology.

Richard Holcomb, PhD is an independent consultant biostatistician. Since 1987, Dr. Holcomb has been a consultant in biostatistics, clinical trials, and regulatory affairs to the US medical device industry; he is also an independent affiliate of Quintiles Consulting.

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[4] Oxford Centre for Evidence-Based Medicine

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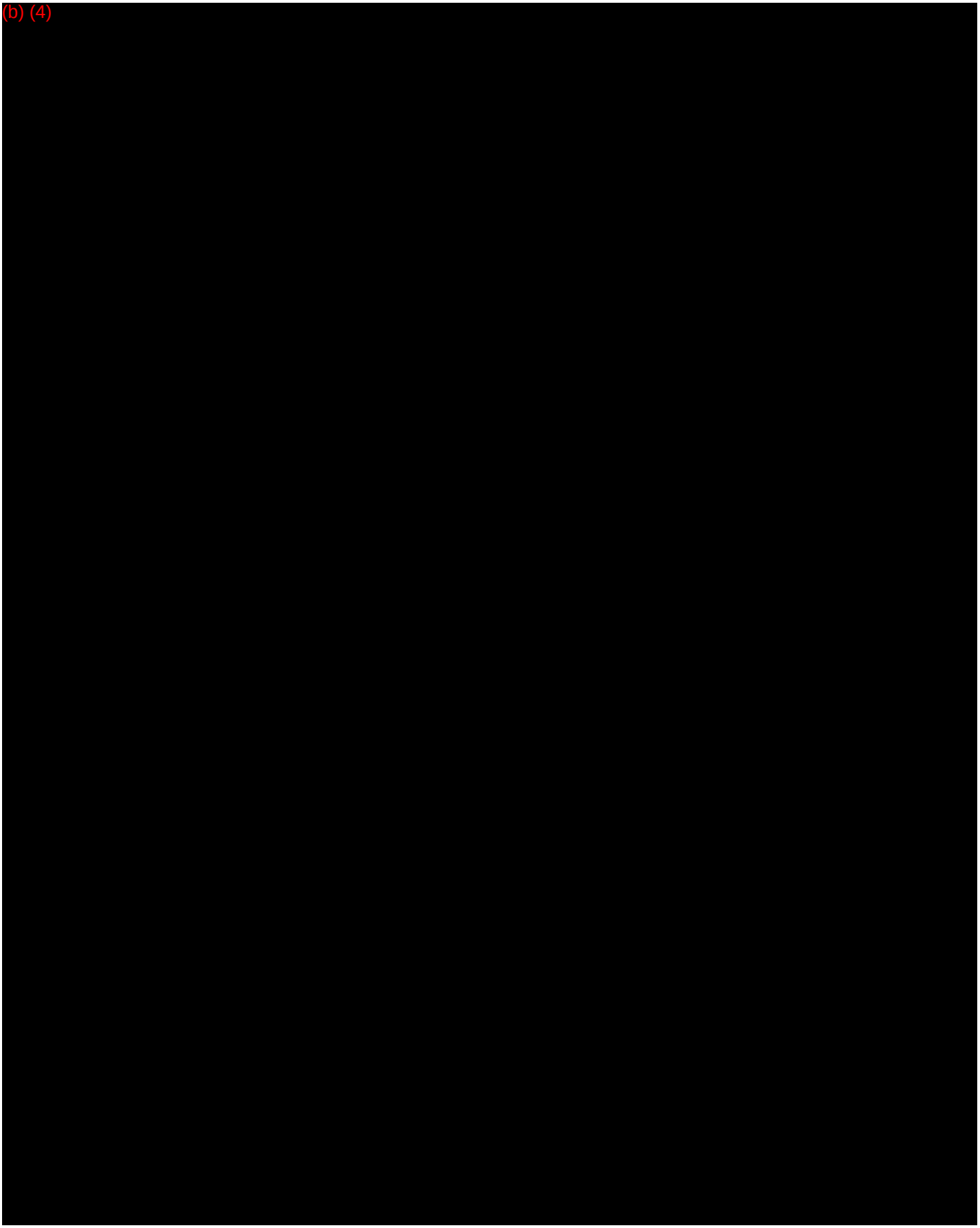

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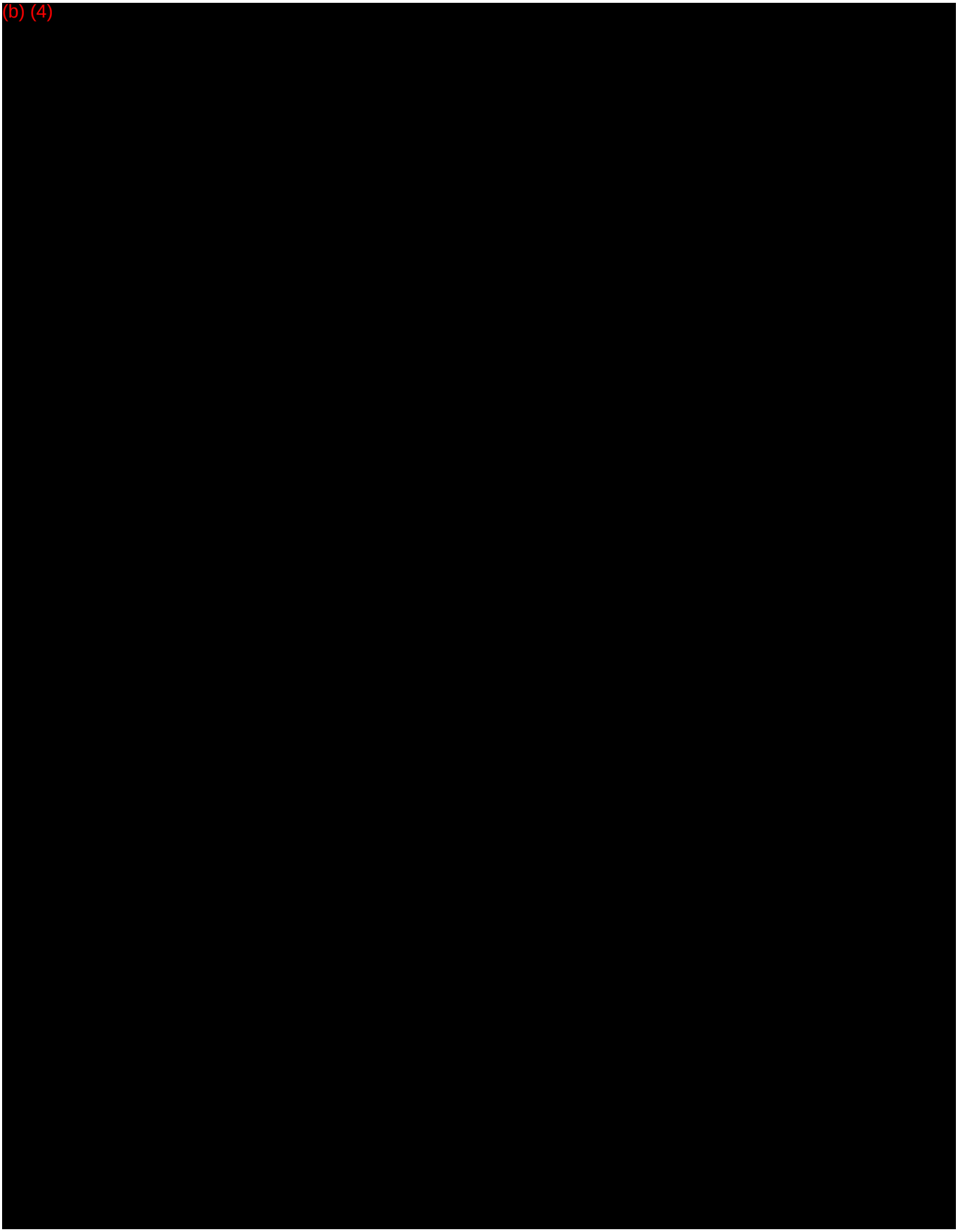

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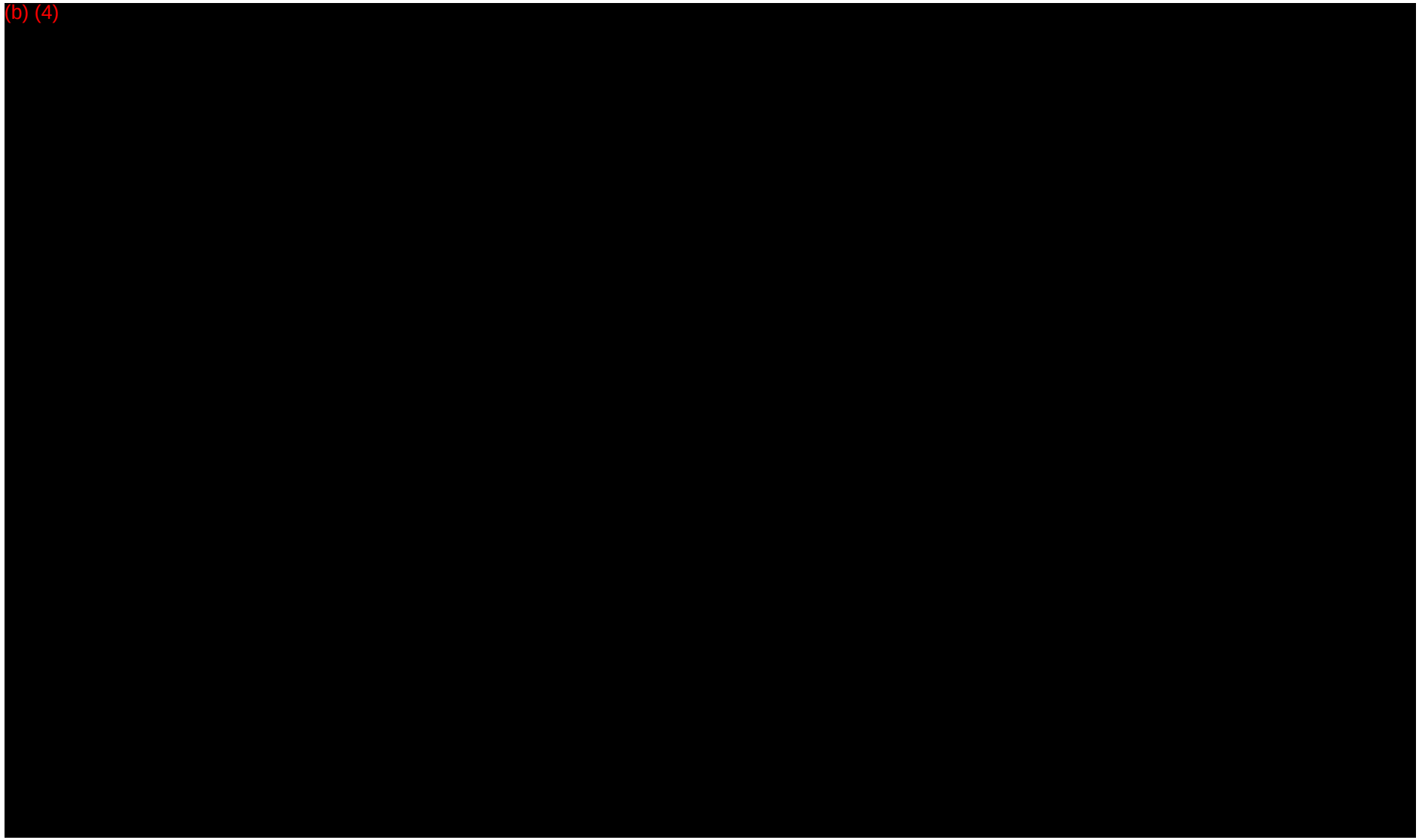

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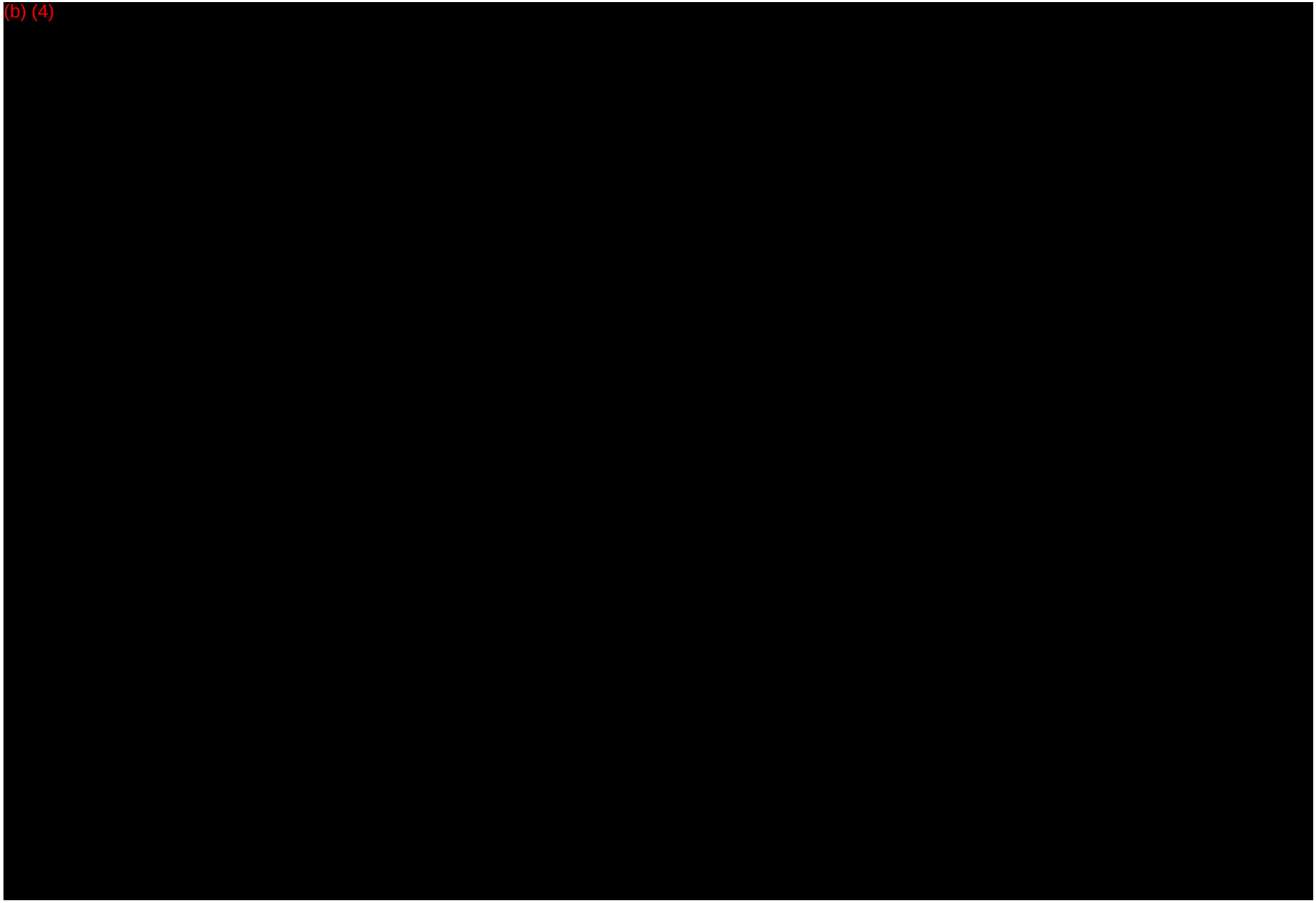

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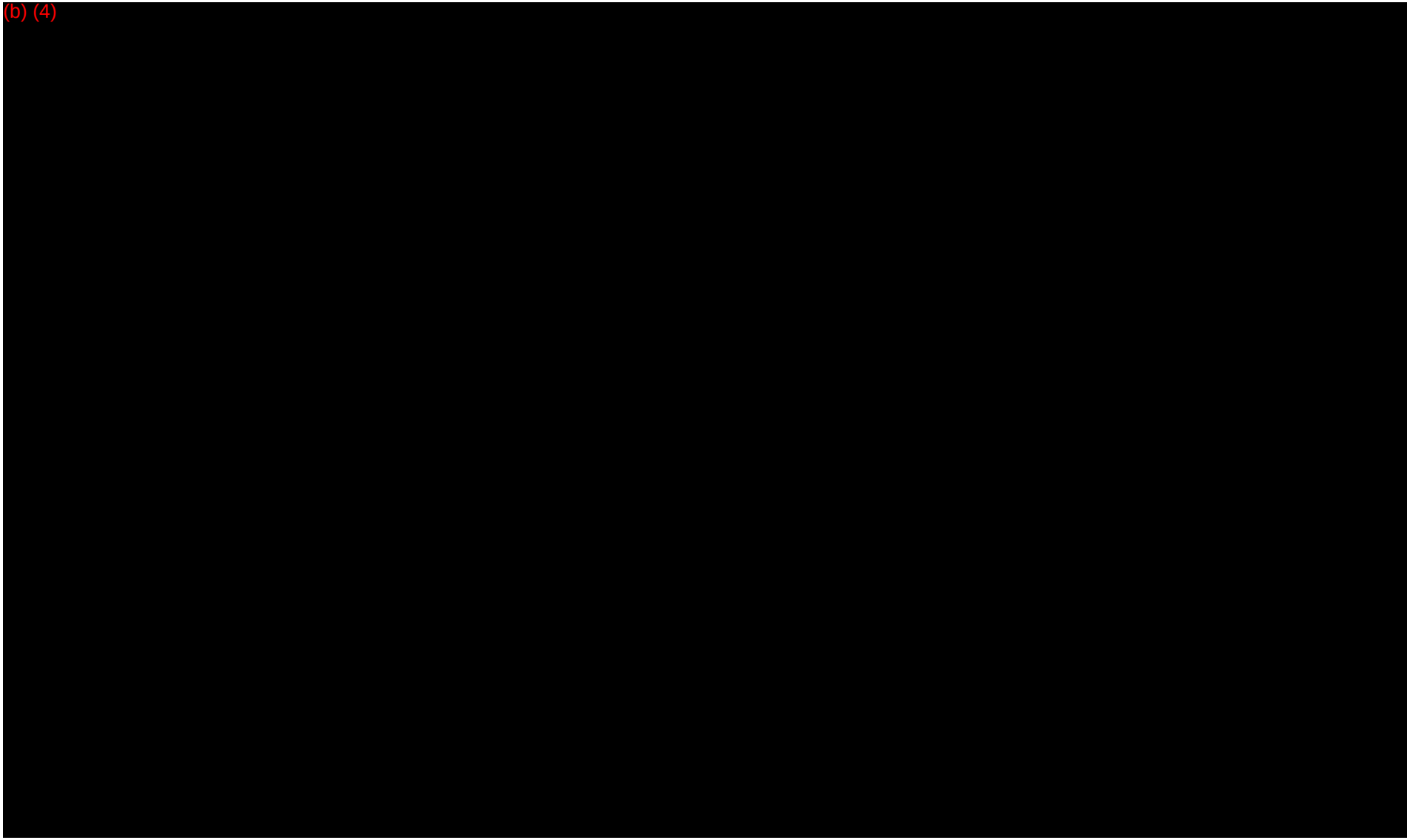

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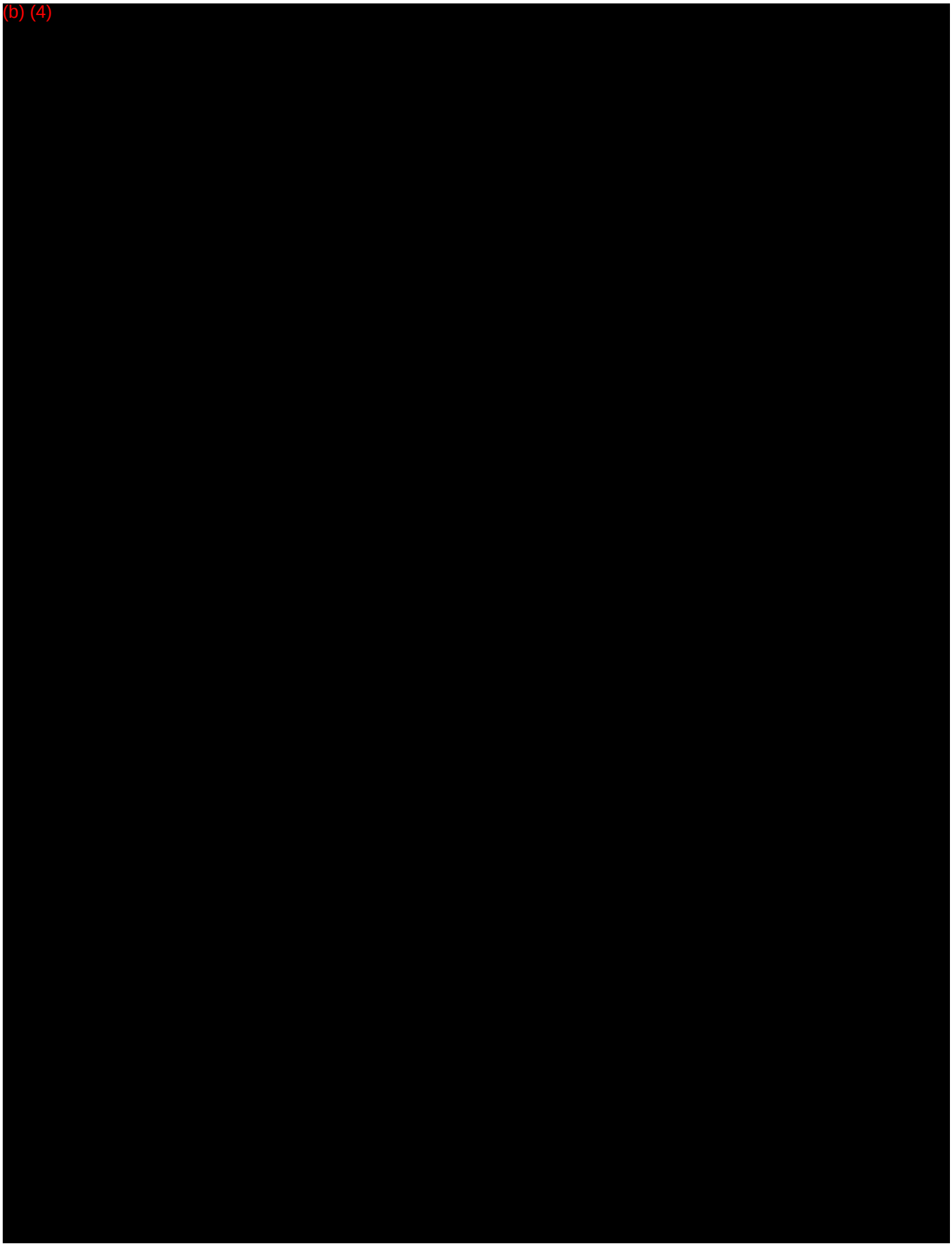

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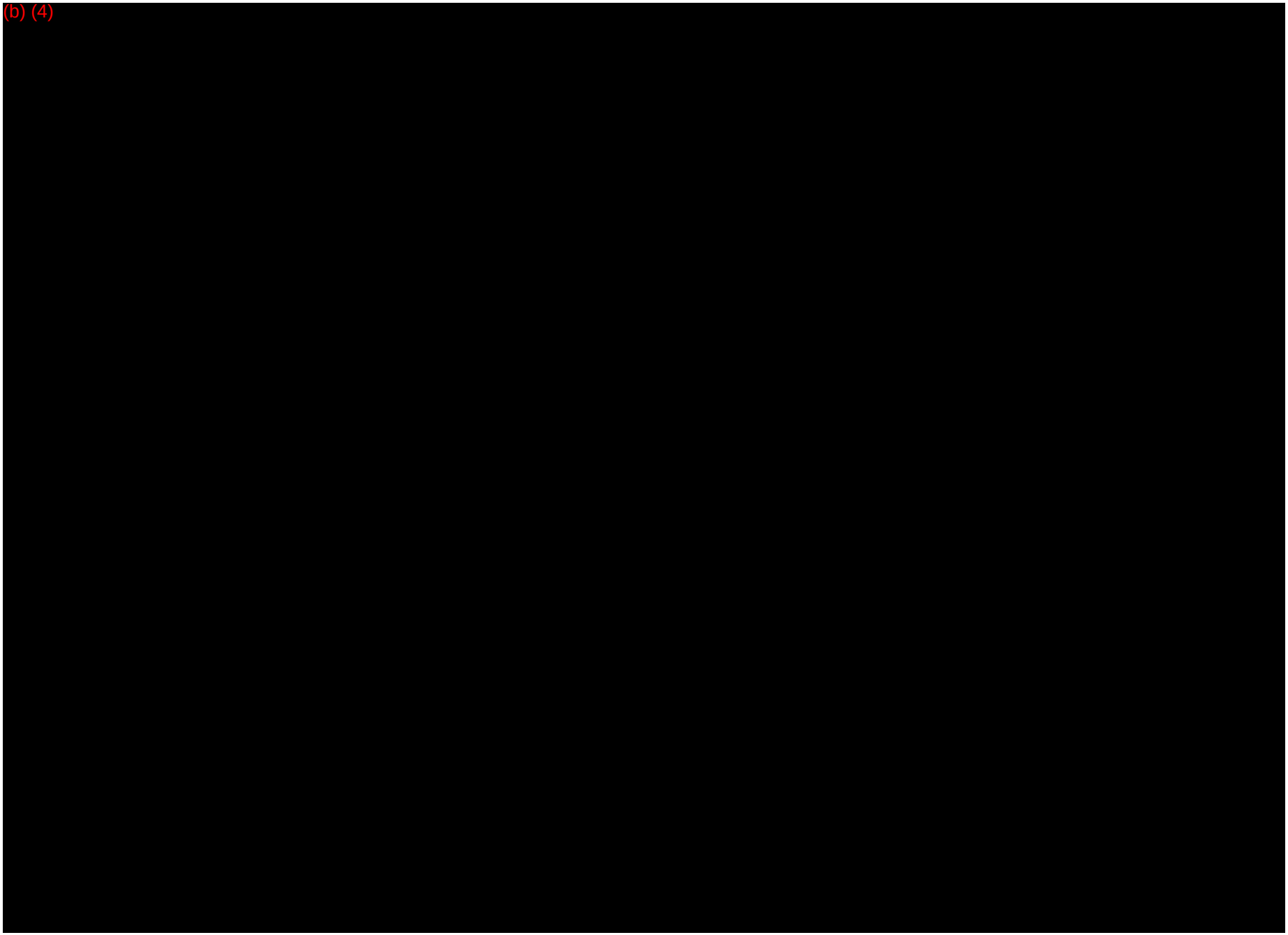

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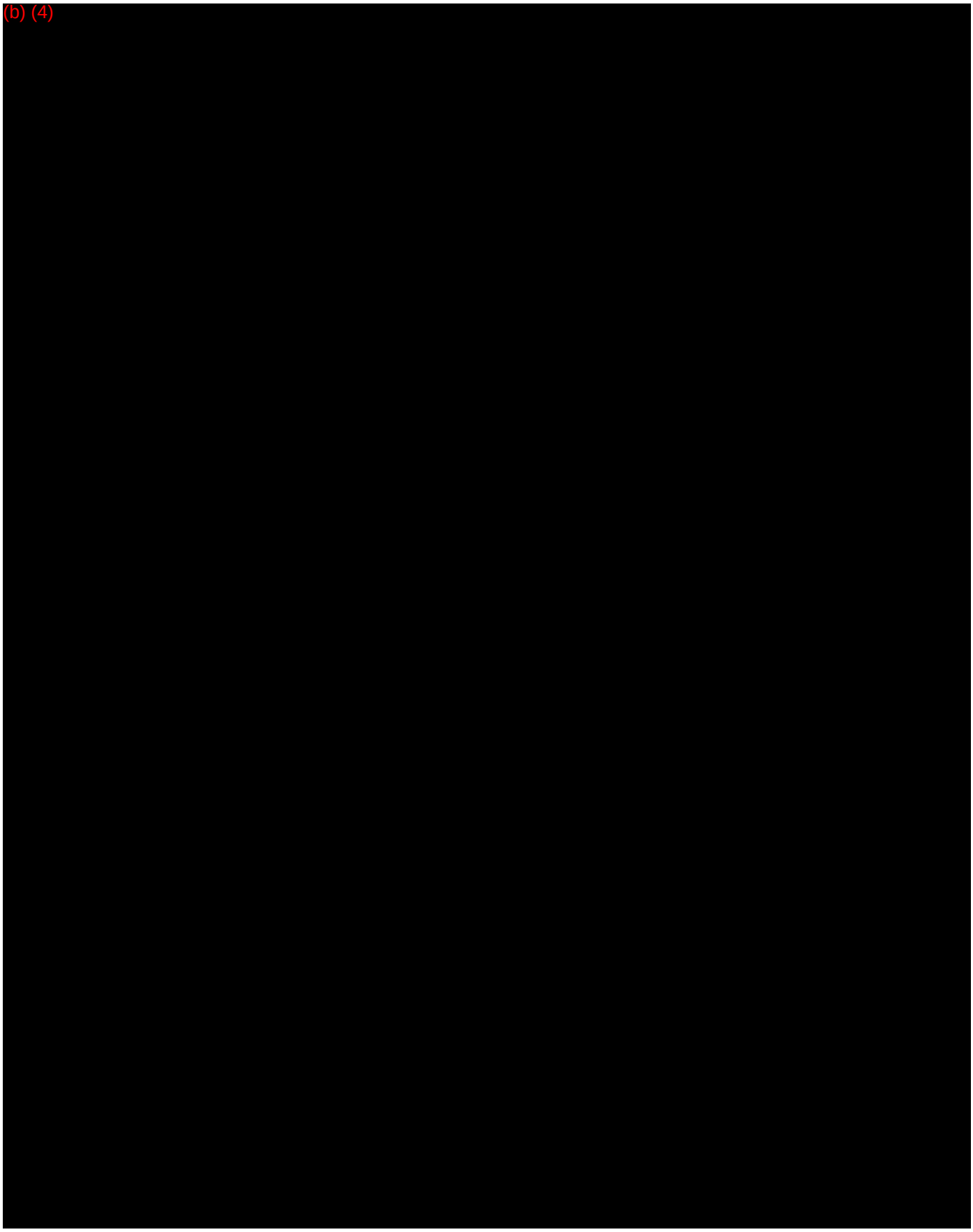

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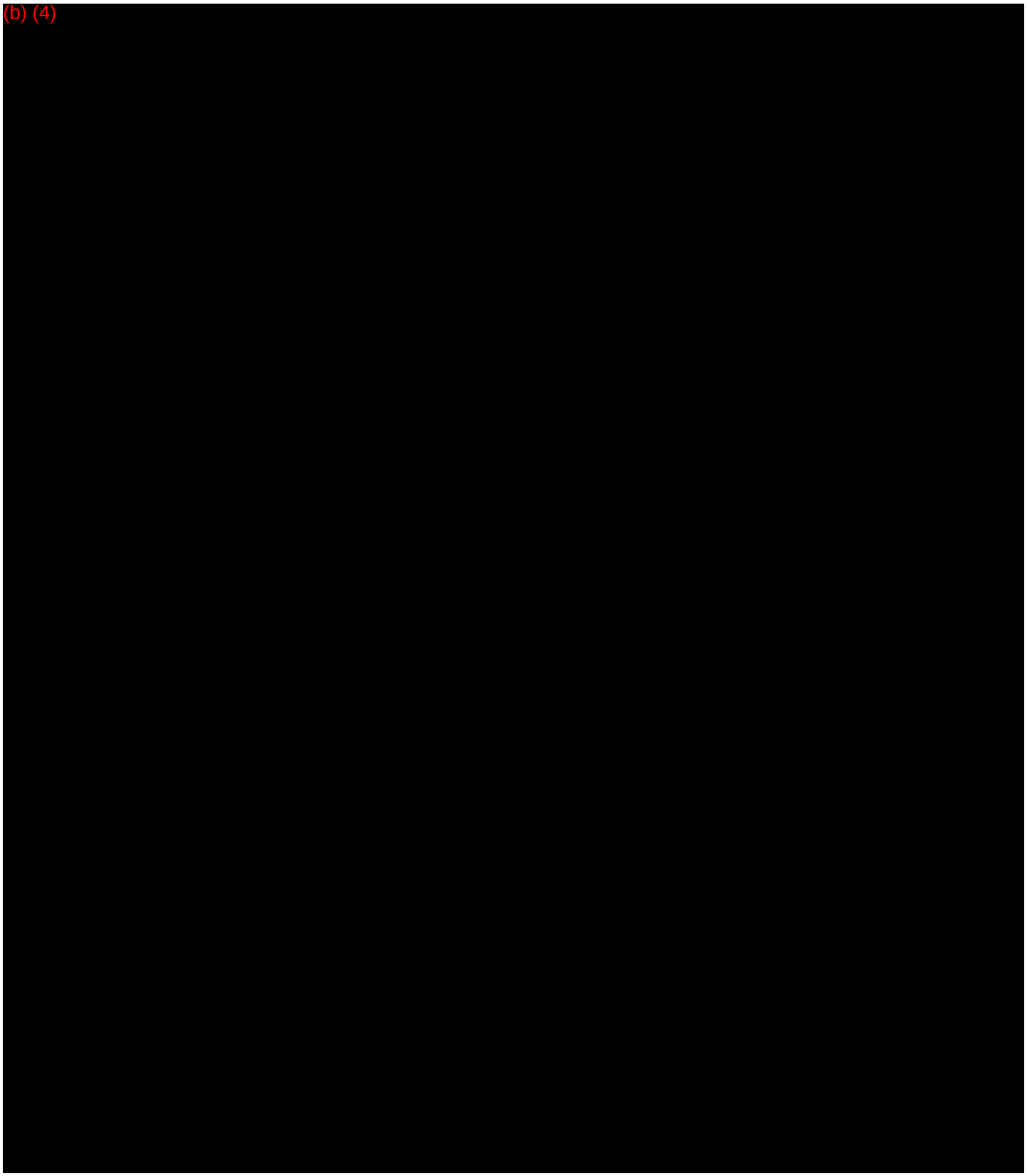

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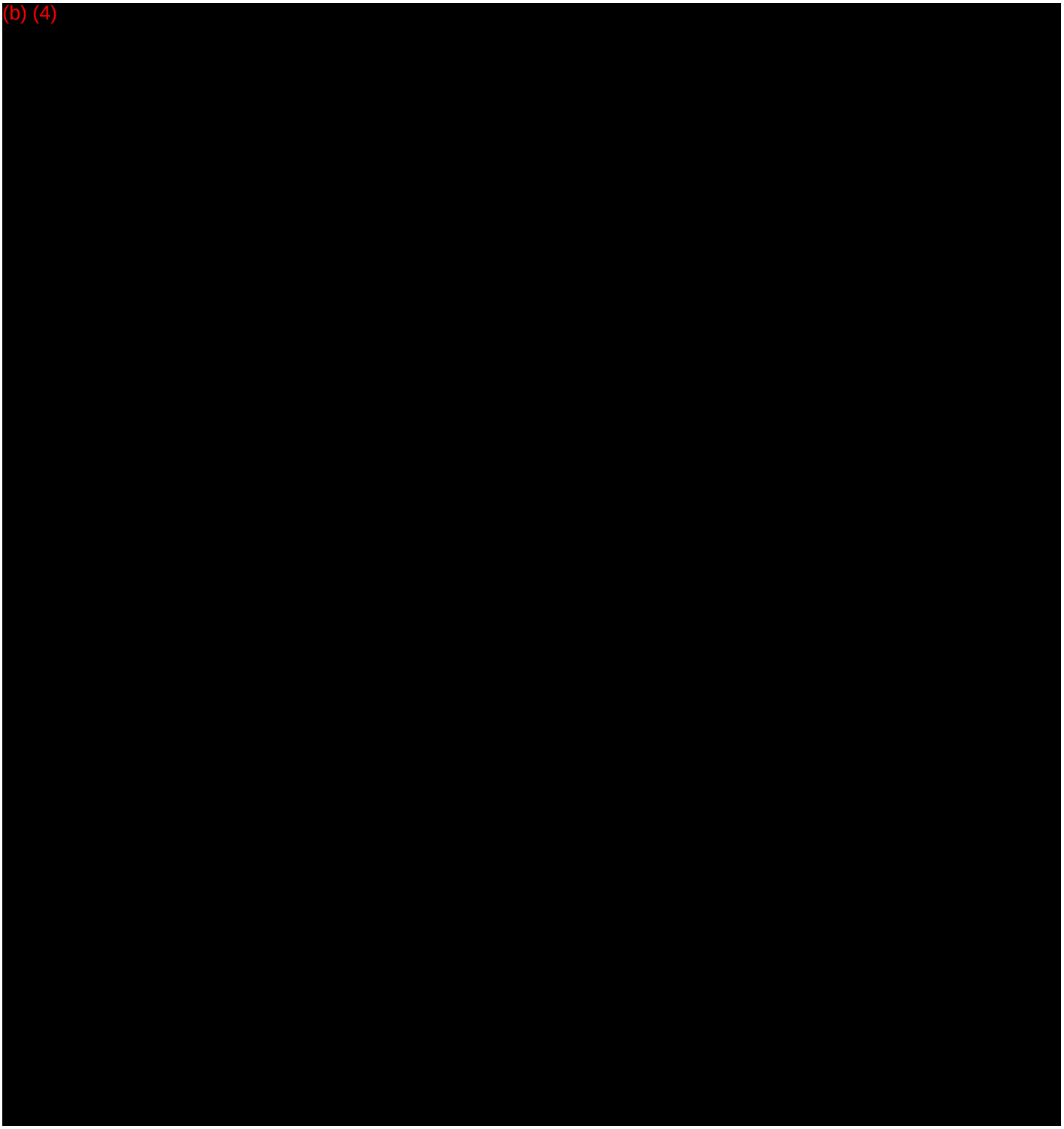

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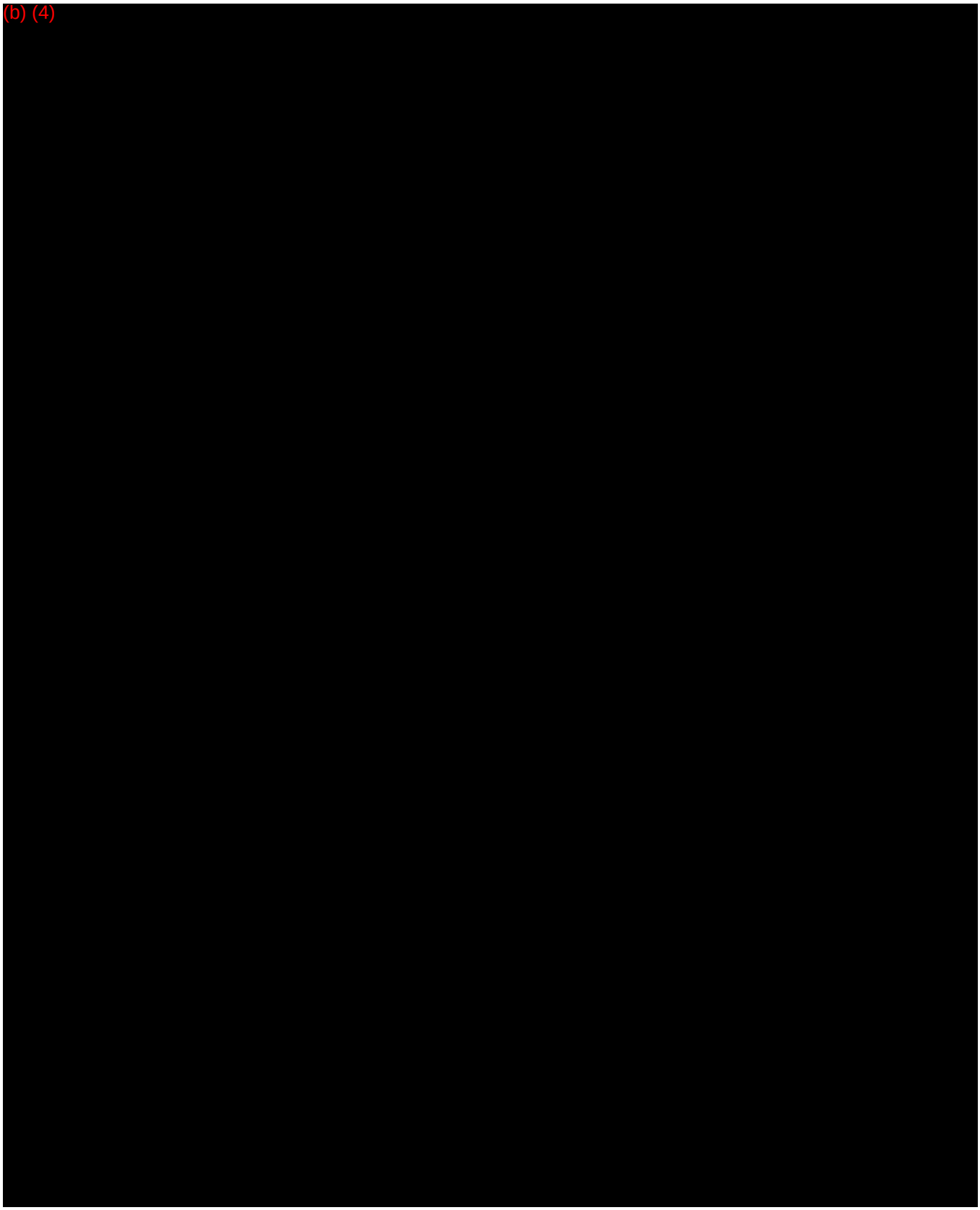

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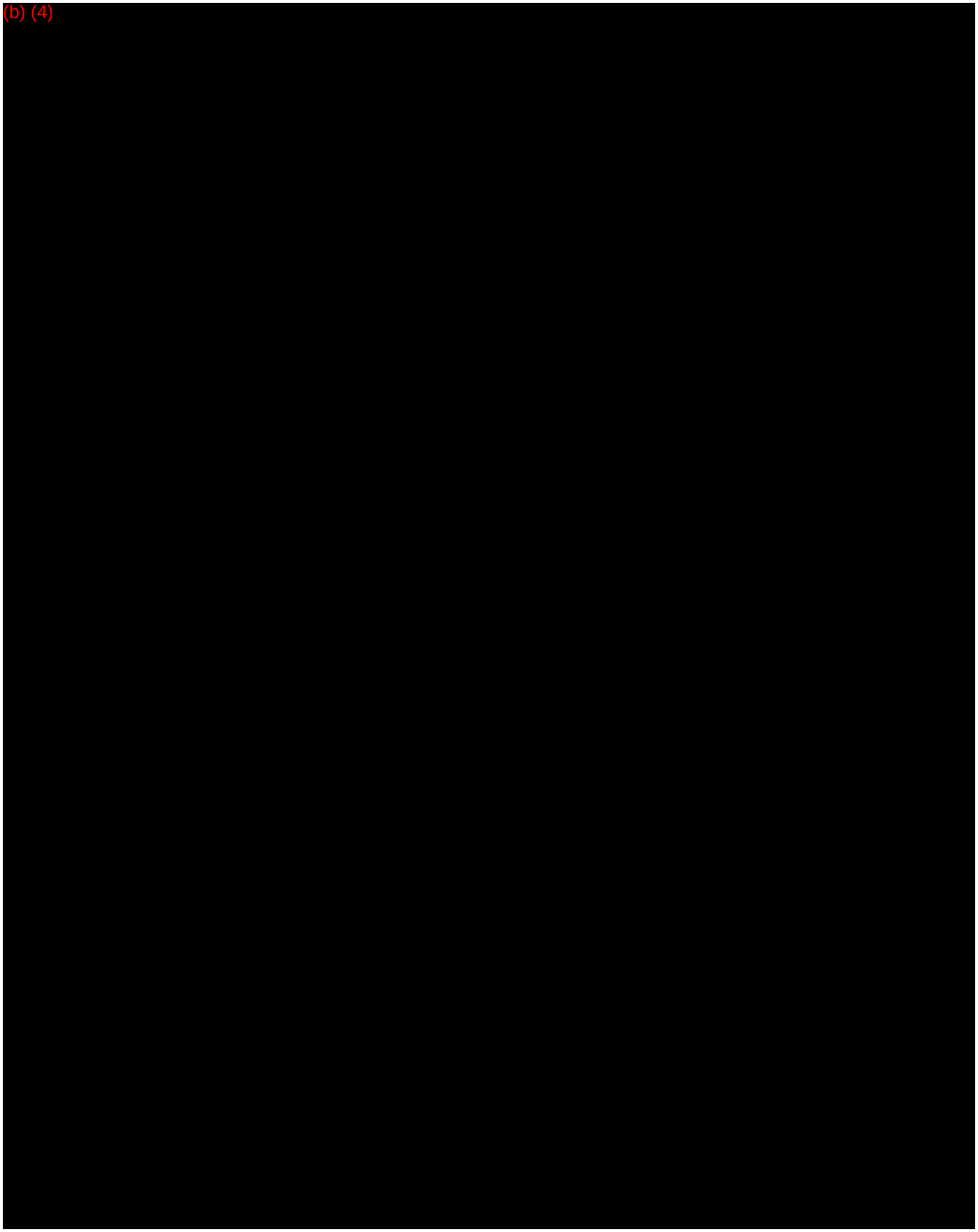

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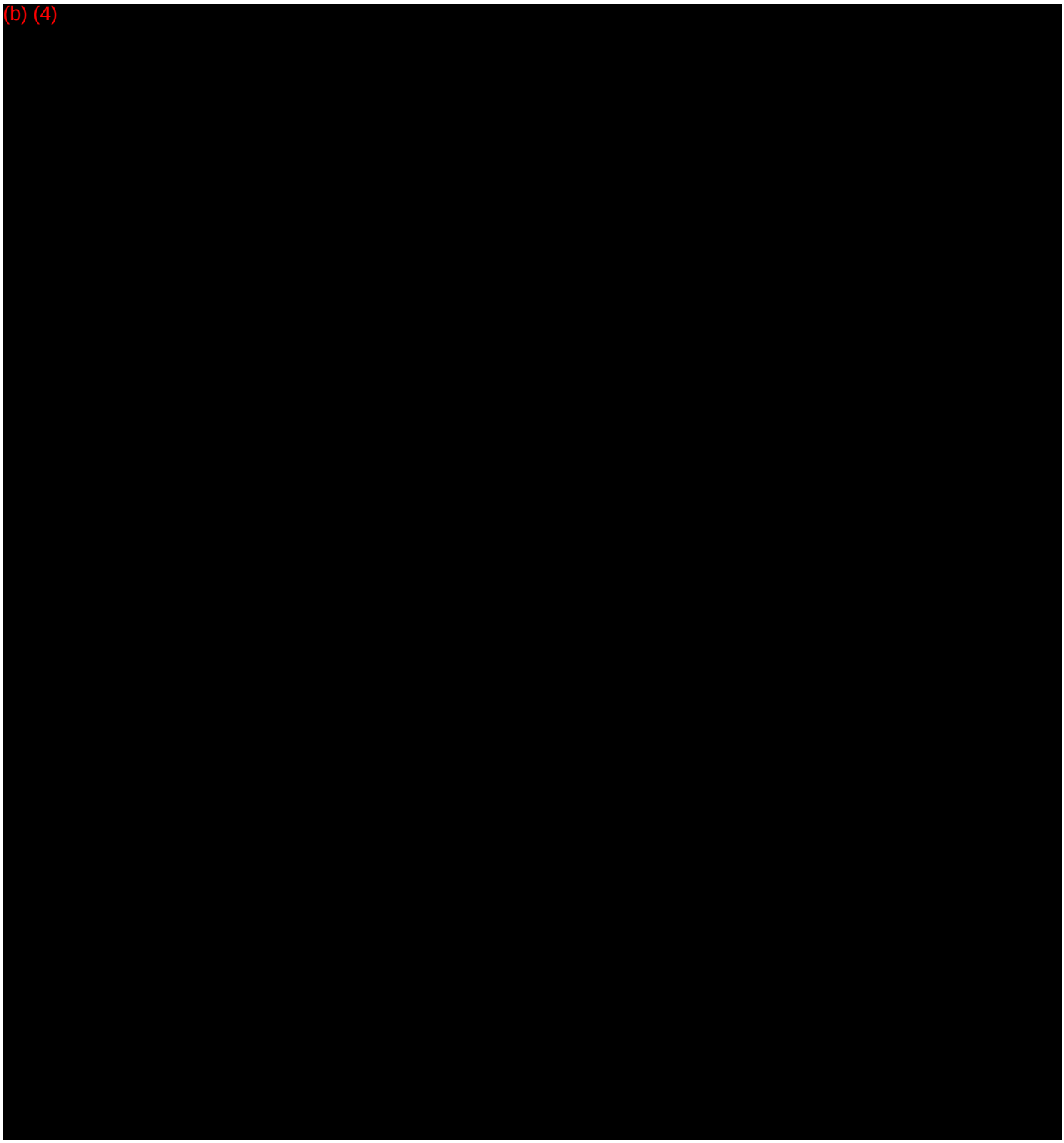

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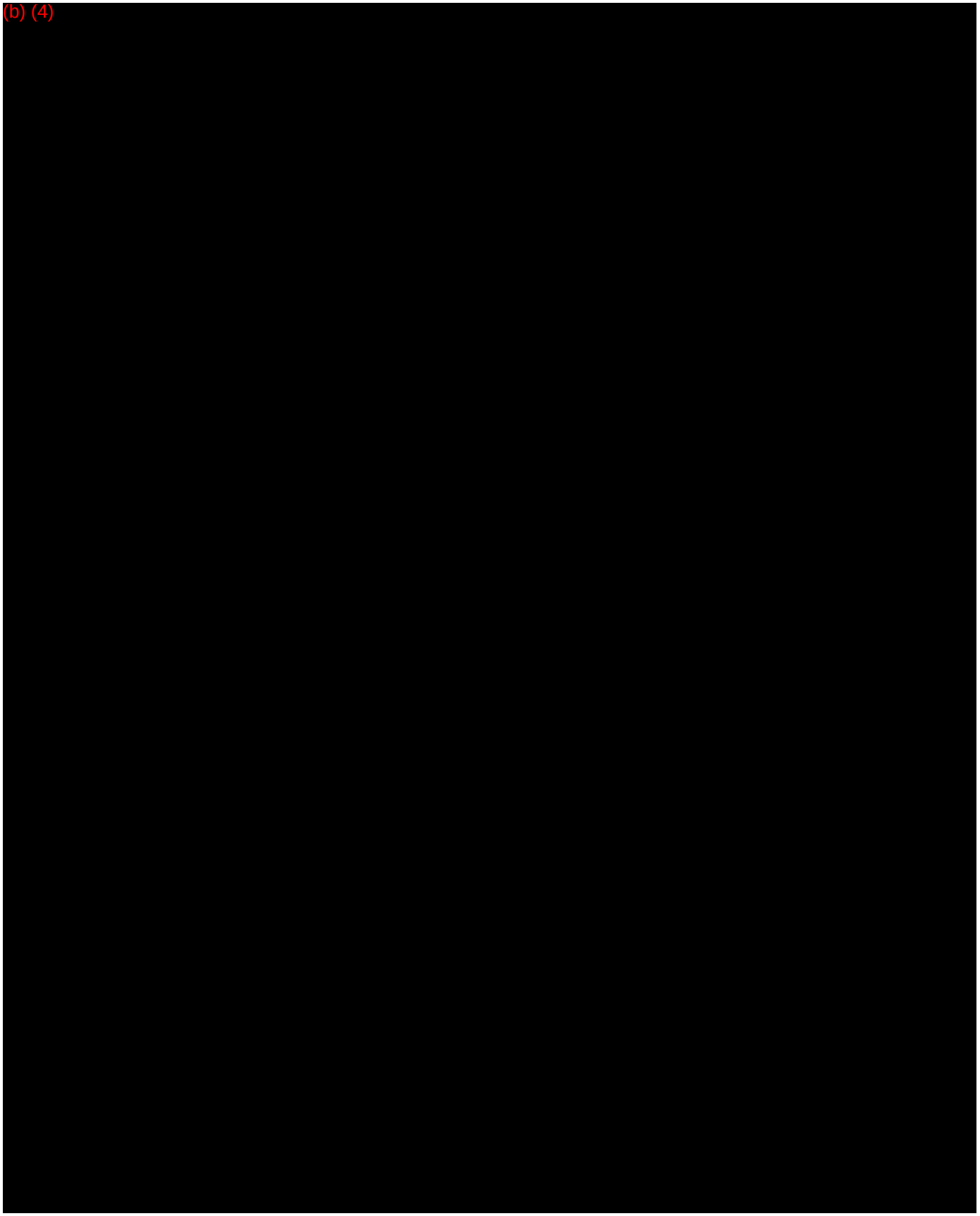

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11.4 Common Adverse Events in WEB-IT

Table 56: Common Adverse Events (≥2 Patients) in WEB-IT

System Organ Class	Preferred Term	AE Rate[a] x/n (%) Events
Non-serious Adverse Events within 30 Days		
All	All	68/150 (45.33) 135
Cardiac disorders	Arrhythmia	2/150 (1.33) 2
Eye disorders	Visual impairment	4/150 (2.67) 4
Gastrointestinal disorders	Abdominal pain	3/150 (2.00) 3
	Nausea	9/150 (6.00) 10
	Vomiting	2/150 (1.33) 2

System Organ Class	Preferred Term	AE Rate[a] x/n (%) Events
General disorders and administration site conditions	Adverse Drug Reaction	7/150 (4.67) 8
	Chest discomfort	2/150 (1.33) 2
	Vessel puncture site bruise	2/150 (1.33) 2
	Vessel puncture site haematoma	4/150 (2.67) 4
	Vessel puncture site pain	5/150 (3.33) 5
Investigations	Blood pressure increased	2/150 (1.33) 2
Metabolism and nutrition disorders	Electrolyte imbalance	2/150 (1.33) 3
Musculoskeletal and connective tissue disorders	Arthralgia	2/150 (1.33) 2
	Back pain	3/150 (2.00) 3
	Neck pain	2/150 (1.33) 2
	Pain in extremity	4/150 (2.67) 4
Nervous system disorders	Headache	20/150 (13.33) 20
	Migraine	2/150 (1.33) 2
	Transient ischaemic attack	3/150 (2.00) 3
Renal and urinary disorders	Urinary retention	2/150 (1.33) 2
Vascular disorders	Arterial thrombosis	2/150 (1.33) 2
	Hypertension	2/150 (1.33) 2
	Vasospasm	5/150 (3.33) 5
Non-serious Adverse Events within 31 Days to 12 Months		
All	All	65/150 (43.33) 151
Cardiac disorders	Angina pectoris	1/150 (0.67) 2
Ear and labyrinth disorders	Vertigo	1/150 (0.67) 2
Eye disorders	Visual impairment	4/150 (2.67) 4
Gastrointestinal disorders	Abdominal pain	1/150 (0.67) 2
	Diarrhoea	1/150 (0.67) 2
	Adverse drug reaction	7/150 (4.67)

System Organ Class	Preferred Term	AE Rate[a] x/n (%) Events
General disorders and administration site conditions		7
	Vessel puncture site haematoma	4/150 (2.67) 4
Infections and infestations	Tooth infection	2/150 (1.33) 2
	Urinary tract infection	3/150 (2.00) 4
	Viral infection	2/150 (1.33) 2
Investigations	Blood pressure increased	2/150 (1.33) 2
Metabolism and nutrition disorders	Electrolyte imbalance	3/150 (2.00) 3
Musculoskeletal and connective tissue disorders	Arthritis	3/150 (2.00) 3
	Back pain	4/150 (2.67) 4
	Neck pain	3/150 (2.00) 3
Nervous system disorders	Headache	20/150 (13.33) 24
	Ischaemic stroke	2/150 (1.33) 2
	Migraine	2/150 (1.33) 2
	Sensory loss	2/150 (1.33) 2
	Transient ischaemic attack	2/150 (1.33) 2
Psychiatric disorders	Anxiety	3/150 (2.00) 3
	Depression	4/150 (2.67) 4
	Insomnia	2/150 (1.33) 2
Vascular disorders	Hypertension	3/150 (2.00) 5

[a]Summing across preferred terms or system organ classes will not result in the same sum overall because of multiple events per patient even in the same preferred term or organ class.