



Level of Evidence to Support Marketing Applications

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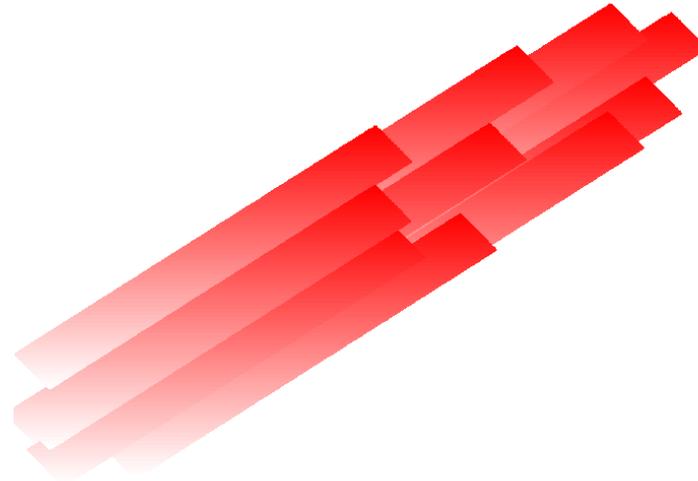
How Much Evidence?

- Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products
- Example: Sanvar (vapreotide acetate) Intravenous Injection
 - Indication: Adjunctive therapy to endoscopic intervention for the control of acute esophageal bleeding as a result of portal hypertension
 - Gastrointestinal Drugs Advisory Committee Meeting; May 19, 2009



Guidance for Industry

Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
May 1998
Clinical 6

1962 Drug Amendments to the FDC Act

Required manufacturers to establish a drug's effectiveness by “substantial evidence”

What is “Substantial Evidence”?

Section 505(d) of the Food and Drug Act:

“Evidence consisting of *adequate and well-controlled investigations*, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that *the drug will have the effect it purports or is represented to have* under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof”

How Many Studies?

- At least two adequate and well-controlled studies, each convincing on its own.
- Broadly interpreted to the extent possible
 - Can rely on information from other adequate and well-controlled studies of other doses and regimens, dosage forms, other populations
 - If no other adequate and well-controlled studies, submitted study must meet a higher standard

Why More Than One Study?

- Any trial may be subject to unanticipated, undetected, systematic biases
- Any trial may have a positive finding due to chance alone - a false positive finding
- Independent substantiation of results helps minimize an erroneous conclusion that a drug is effective

When May a Single Adequate and Well-Controlled Study be Sufficient?

- Generally limited to situations where an adequate and well-controlled trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with a potentially serious outcome *AND*
- A second adequate and well-controlled trial would be practically or ethically impossible

Review Considerations when Relying on a Single Adequate and Well-Controlled Study

- Large multicenter study
 - No single site provides an unusually large fraction of the patients
 - No single investigator or site is disproportionately responsible for the effect seen
- Consistency across study subsets
- Clinically meaningful
- Multiple endpoints involving different events
- Statistically very persuasive finding
 - Two-sided: $p < 0.00125$
 - Not enough by itself

What is an Adequate and Well-Controlled Trial?

(21 CFR 314.126):

“A design that permits a valid comparison with a control to provide a quantitative assessment of drug effect”

- Review issues
 - Type of control
 - Assignment of subjects
 - Minimizing bias

Choice of Control: Historical Controls

21 CFR 314.126 (v):

The results of treatment with the test drug are *compared* with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, *in comparable patients or populations*.

Choice of Control: Historical Controls

(21 CFR 314.126 (v))

- Usually reserved for special circumstances
- Examples include studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).

Assigning Patients to Treatment Groups

(21 CFR 314.126 (b))

- The method minimizes bias
- Assures comparability of the groups with respect to pertinent variables

Minimize Bias

- Adequate measures are taken to minimize bias on the part of
 - Subjects
 - Observers
 - Analysts of data
- Examples of procedures used to accomplish this
 - Randomization
 - Double-blinding

Sanvar (vapreotide acetate) Intravenous Injection

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Acute Esophageal Bleeding (EVB)

- “EVB is a rare (orphan) disease
- EVB is a serious and life-threatening complication of portal hypertension in patients with cirrhosis
- EVB requires emergency medical intervention and, despite important advances in therapy, is associated with a high morbidity and mortality
- There is no vasoactive drug approved for this indication in the US”

Source: Debiovision, Inc.; Slides for the May 19, 2009 meeting of the Gastrointestinal Drugs Advisory Committee (available online)

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Acute Esophageal Bleeding Treatment Modalities

Practice guidelines recommend band ligation as the endoscopic treatment of choice for the prevention and management of gastroesophageal varices and acute variceal bleeding.

Source: FDA Slides for the May 19, 2009 meeting of the Gastrointestinal Drugs Advisory Committee (available online)

Regulatory History of Sanvar

- February 2004: NDA 21-761 submitted with three randomized controlled trials:
 - Egypt (negative, single center, small)
 - Hong Kong (negative)
 - France (positive, not robust) – VAP-14

Source: FDA Slides for the May 19, 2009 meeting of the Gastrointestinal Drugs Advisory Committee (available online)

Control of bleeding and survival at 5 days

Study	Response Rate		Sanvar-Placebo	P-value
	Sanvar	Placebo		
VAP-14 (France) 1997-1998	66% (65/98)	50% (49/98)	16%	p=0.02
VAP-07 (Egypt)* 2002 *single center	71% (22/31)	59% (16/27)	12%	p=0.35
VAP-02 (Hong Kong) 1997-2001	55% (28/51)	51% (26/51)	4%	p=0.69

Study VAP-14 (France)

- Primary efficacy results
Sanvar vs Placebo:
 - 66% vs 50% ($p=0.021$)
- One center had:
 - The most patients (14%)
 - Lower proportion of Child Class C patients
 - Imbalance of small varices in the Sanvar group

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Regulatory History of Sanvar

- December 2004:
 - Approvable action
 - Additional efficacy data needed
- Another study (VAP-06) was ongoing but efficacy results were not available

Source: FDA Slides for the May 19, 2009 meeting of the Gastrointestinal Drugs Advisory Committee (available online)

Regulatory History after Approvable Action

- Preliminary results of VAP-06 did not show superiority of Sanvar over Placebo
- FDA recommended another randomized controlled trial
 - Applicant made a case that a placebo-controlled trial could no longer be conducted

Source: FDA Slides for the May 19, 2009 meeting of the Gastrointestinal Drugs Advisory Committee (available online)

Regulatory History of Sanvar

- Second submission
 - VAP-301 (United States)
 - Single arm, open label
 - No placebo arm
 - Historical control
 - VAP-06 (Eastern Europe) – not statistically significant
 - Meta-analysis – not a substitute for an adequate and well-controlled study

Source: FDA Slides for the May 19, 2009 meeting of the Gastrointestinal Drugs Advisory Committee (available online)



Studies Submitted in 2008

Study	Design	N	Cause of Cirrhosis
Original Submission			
VAP-14 (France; 1997-1998)	R, DB, PC	196	Etoh (85%)
VAP-07 (Egypt; 2002)	R, DB, PC (single center*)	58	Hepatitis associated with schistosomiasis (83%)
VAP-02 (Hong Kong; 1997-2001)	R, DB, PC	102	Etoh (38%); Viral H. (45%)
Current Submission			
VAP-06 (E. Europe; 2003-2004)	R, DB, PC	267	Etoh (62%); Viral H. (38%)
VAP-301 (U.S.; 2006-2008)	Open-label, Single-arm	70	Etoh with Viral H. (29%); Etoh (31%); Viral H. (14%)

*VAP-07 single-center (all other multi-center)

R: Randomized; DB: Double-Blind; PC: Placebo-controlled

Sanvar

VAP-301

- Design
 - Open-label single-arm study (n=70)
 - Qualitative comparison to VAP-14
- Concerns
 - Open label
 - Appropriate historical control
 - Different endoscopic treatment used

Sanvar

VAP-301

- Validity of historical comparison
- Contribution of band ligation to success rate

Baseline Characteristics

		VAP-301	VAP-14	
		Sanvar (N=70)	Sanvar (N=98)	Placebo (N=98)
Etiology of PHT*	Etoh	33%	84%	86%
	Viral hep.	14%	3%	3%
	EtOH + Viral hep.	29%	10%	7%
Known Previous History of:	Ascites	57%	37%	33%
	Hepatic Encephalopathy	20%	14%	21%

*Other etiologies for 17 pts in VAP-301 group, 2 in VAP-14 Vap group, and 4 in VAP-14 Plac group

Baseline Characteristics

		VAP-301	VAP-14	
		Sanvar (N=70)	Sanvar (N=98)	Placebo (N=98)
Child Class*	A-B	62%	61%	59%
	C	38%	39%	41%
Variceal size	< 5 mm	10%	31%	28%
	> 5 mm	90%	69%	72%
Previous episodes of EVB	1 episode	23%	19%	18%
	2 episodes	7%	9%	7%
	3+ episodes	4%	10%	13%

*N=69 for VAP-301, N=92 for VAP-14 Sanvar, and N=94 for VAP-14 Placebo (Child-Pugh Score available for 69 pts in VAP-301, for 92 in VAP-14 Sanvar, and for 94 in VAP-14 Placebo.)

Endoscopic Treatment Modalities

	VAP-301	VAP-14	
	Sanvar (N=70)	Sanvar (N=98)	Placebo (N=98)
Band Ligation	86%	31%	31%
Sclerotherapy	4%	50%	56%

Percentages are for band ligation only or sclerotherapy only

VAP-301: Both (6%); None (4%)

VAP-14 (Vap): Both (1%); None (9%); Glue (6%); Other (1%); No EGD (2%)

VAP-14 (Plac): Both (1%); None (7%); Glue (1%); Band+Glue (1%); Other (1%); No EGD (2%)

Emergency Banding Ligation vs. Sclerotherapy for the Control of Active Bleeding from Esophageal Varices (Lo et al., 1997)

	Band Ligation (N=37)	Sclerotherapy (N=34)
Control of bleeding (for 72 hours)	97%	76%
Re-bleeding (within 1 month)	17%	33%
Units of Blood Transfused (Mean ± SD)	3.2 ± 1.2	4.5 ± 1.8
Mortality (1 month)	19%	35%

Results

Efficacy Criteria	VAP-301	VAP-14	
	Sanvar (N=70)	Sanvar (N=98)	Placebo (N=98)
Control of bleeding at the end of the 5 day infusion and survival (ITT)	77% (54)	66% (65)	50% (49)

Survival

	VAP-301	VAP-14	
	Sanvar (N=70)	Sanvar (N=98)	Placebo (N=98)
Day 5	90% (63)	95% (93)	93% (91)
Day 42	74% (52)	86% (84)	79% (77)

*ITT population

Summary

- Observed Response Rate:
 - **77%** (VAP-301) vs. **50%** (VAP-14 Placebo)
- Endoscopic Treatment Modality:
 - Band ligation: 86% vs. 31%
- Baseline Characteristics:
 - Varices > 5 mm: 90% vs. 72%
 - Alcohol + Viral hepatitis: 29% vs. 7%
 - Child Class C: 38% vs. 41%

Collective Evidence

- First submission
 - Only 1 of 3 studies was statistically significant, but was not persuasive
- Second submission
 - One study with a historical control
 - Populations differed
 - Medical practice changed (endoscopic techniques, resuscitation methods)
 - One study with negative findings
 - Meta-analysis can not substitute for an adequate and well-controlled study

Collective Evidence

- Primary endpoint used in studies
 - Baveno III (Consensus Conference, 2000)
 - Composite for control of bleeding at 5 days
 - Components vary by time and include:
 - Blood pressure
 - Transfusion requirement
 - Heart rate
 - Hematocrit
 - Survival
 - Rebleeding
- Baveno IV (Consensus Conference, 2004)
 - “Given the lack of validated parameters to define failure, these new criteria are necessarily arbitrary and must be validated in future studies” (Franchis, J of Hepatology 43:167-176, 2005)
 - Fewer components – removed heart rate and blood pressure

Advisory Committee

- Studies did not provide substantial evidence of efficacy.
- There have been changes in clinical practice in the management of variceal bleeding that impacts study methodology.
- Reanalyze current data to more closely examine if there is a heart rate effect and also determine if there is a certain subgroup of patients which shows a clear benefit (e.g., Child's class A-B).
- There are still limited data on safety and no adequate control data.

Source: Minutes for the May 19, 2009 Meeting (available online)

Summary

- Single and adequate well-controlled studies are possible
- Historic controls are possible
 - Well-defined endpoint
 - Consistent patient populations
 - Consistent medical practice
 - Documentation of natural history
 - Safety data

References

- Guidance Documents
 - Center for Drugs
www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
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