

NDA 22-349
AI-700 - Injectable Suspension
[Perflubutane Polymer Microspheres]

FDA Overview

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FDA Overview

- **Introduction**

- **Supportive Studies**

 - **04** *Safety*

 - **20**

 - **21**

} *Value of contrast vs non-contrast echo*

- **Phase 3 Studies**

 - **32**

 - **33**

} *Safety and Efficacy*

- **Summary**

AI-700

- **Particles of ~ 2 micron for IV injection**
 - **traverse vascular system**
 - **provide acoustic signal for blood**
 - **shell: phospholipid and poly-glycolide**
 - **gas: perflubutane**
- **Elimination:**
 - **gas: exhaled**
 - **particulates: reticuloendothelial system**

Proposed Indication

“AI-700 is an ultrasound imaging agent indicated for patients with stable chest pain being evaluated for inducible ischemia for the detection of coronary artery disease (CAD) based on assessment of myocardial perfusion and wall motion. AI-700 echocardiography is accomplished with rest and stress techniques.”

screening tool to assist the clinician in stratifying patients for referral to coronary arteriography

Study 04

- **Assessed:**
 - **Inflammatory biomarkers**
 - **Immunoreactivity**
- **12 Healthy volunteers**
- **Stage 1: AI-700 injection or placebo**
- **Stage 2: > one year later**
 - **Skin test**
 - **Second AI-700 or placebo injection**

Study 04

C3a Concentrations (mg/mL) Relative to AI-700 Exposure (0.08 mL/kg)

Time point	Stage 1 n = 10	Stage 2 n = 7
- 10 min	31 (29)	69 (42)
6 min	442 (451)	342 (236)
30 min	124 (135)	154 (58)
120 min	44 (22)	76 (31)

Normal C3a < 940 ng/mL
Shown are mean and SD

Study 04

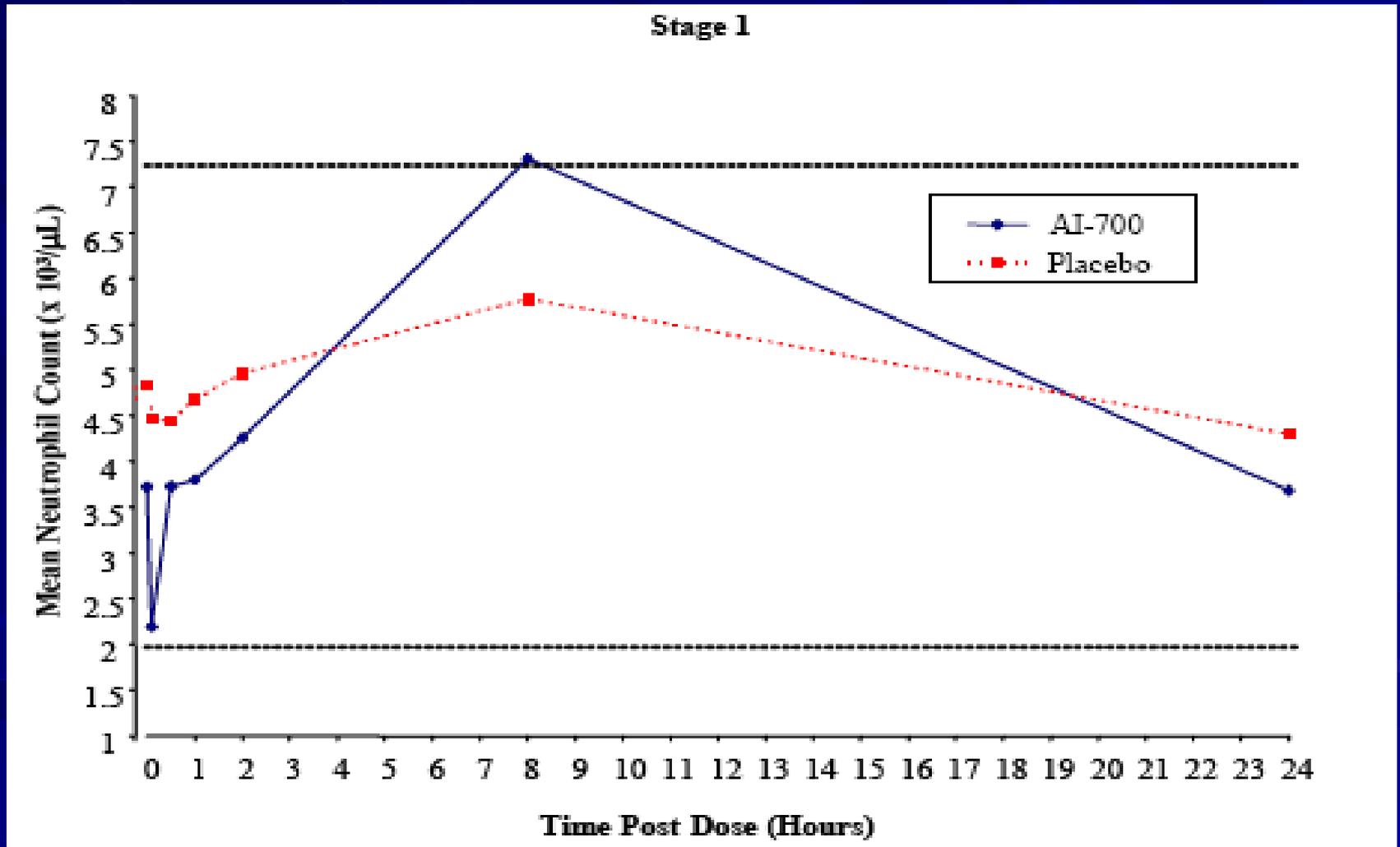
C-Reactive Protein (mg/dL) Relative to AI-700 Exposure

Time point	Stage 1 n = 10	Stage 2 n = 7
- 10 min	0.13 (0.2)	0.14 (0.1)
120 min	NA	0.14 (0.1)
24 hrs	0.58 (0.3)	NA

Normal CRP ≤ 0.29 mg/dL
Shown are mean and SD
NA = not assessed

Study 04

Mean Neutrophil Counts



Study 04

- **AI-700 at a dose of 0.08 mL/kg (twice proposed market dose) caused asymptomatic:**
 - **C3a/complement activation**
 - **C-reactive protein increases**
 - **WBC count alterations**
- **Biomarkers not assessed in patients at proposed marketing dose**

Diagnostic Value of AI-700 Contrast

- **Rest and stress echo wall motion (WM) abnormalities may signal disease, even without contrast**
- **Added value of contrast?**
- **Phase 3 studies evaluated WM and myocardial perfusion together**
- **Studies 20 and 21**

Study 20

- **Exploratory study**
- **Did not utilize stress component (could only detect fixed defects)**
- **Evaluated AI-700 doses higher than proposed marketing dose (0.05 mL/kg or 0.08 mL/kg)**
- **Provided no information regarding “added value” of AI-700 to non-contrasted rest/stress echocardiography**

Study 21

- **3 stages/patients with known or suspected CAD in stages 2 and 3**
- **Rest and dipyridamole stress echo and SPECT**
- **Stage 2: placebo or lower/higher AI-700 doses**
- **Stage 3: market-applicable AI-700 dose**

Study 21 Performance Characteristics

Stress CE vs. Stress SPECT

Dose group	n	Sens	Spec	Agreement
AI 0.01 mL/kg	25	63%	82%	76%
AI 0.05 mL/kg	28	62%	93%	79%
AI ~ 0.04 mL/kg	22	33%	88%	73%
Placebo	22	43%	80%	68%

Majority read summary of echo results

Phase 3 Studies: Study 32 and 33 Similar Design Features

- **Single arm, multicenter**
- **Each center qualified in Study 23 (pilot)**
- **Rest/stress (dipyridamole) ECHO & SPECT**
- **AI-700 0.04 mL/kg over \leq 10 mins (2 doses)**
- **Primary endpoint: performance characteristic comparison of ECHO & SPECT**
- **“Truth standards” for CAD presence/absence**
- **Central image assessment, w/o clinical data**

Studies 32 and 33

Unique Design Features

	32	33
Eligibility:	Chest pain + SPECT	Chest pain + coronary angio completed/scheduled
SPECT Reads	1 reader	3 readers
Truth Std	coronary angio or clinical history	coronary angio* or clinical history

*** plan for 33 anticipated most patients
would have coronary angio**

Study 32 & 33

Primary Endpoints Evolved

- **Original: estimates of sens/spec of ECHO vs truth standard (ANGIO/SPECT/clinical)**
- **Modified based on FDA recommendations:**
 - **Hypothesis testing**
 - **Sens/spec comparison of ECHO to SPECT**
 - **Non-inferiority design with performance expectations for SPECT**

Study 32 & 33 Primary Analyses

- **“Sequential non-inferiority analyses will be performed for ECHO versus SPECT:
 - first for accuracy
 - followed by sensitivity and specificity”**
- **“If the accuracy endpoint is met, similar analyses will be performed for sensitivity and specificity.”**
- **Accuracy/sens/spec in the mITT population for each of 3 AI-700 readers**
- **Success: if lower bound of 2-sided 95% CI for relative risk ratio (echo/SPECT) is > 0.83 for at least 2 of the 3 AI-700 readers**

Study 33 Conduct

- **Study 32 AI-700 findings available prior to completion of Study 33 echo reads**
- **Study 33 echo reads halted/readers retrained to enhance disease detection**
- **Retraining performed prior to any analyses**

Baseline Characteristics

<i>Characteristic</i>	Study 32 n = 321	Study 33 n = 457
Age (yrs, mean)	61	62
Male	67%	80%
Caucasian/white	61%	79%

Patient Disposition & CAD Prevalence

<i>Group</i>	Study 32	Study 33
Enrolled	321	457
mITT	285	377
Excluded from mITT	36	80
CAD prevalence in mITT group	44%	58%

Study 32 Primary Analyses

	SPECT	Echo #1	Echo # 2	Echo # 3
Accuracy	70%	66%	67%	71%
<i>RR ratio CI LB</i>		0.86	0.87	0.93
Sensitivity	78%	77%	57%	50%
<i>RR ratio CI LB</i>		0.88	0.63	0.54
Specificity	64%	58%	75%	88%
<i>RR ratio CI LB</i>		0.78	1.04	1.24

Study 33 Primary Analyses

	SPECT	Echo #1	Echo # 2	Echo # 3
Accuracy	67%	66%	70%	70%
<i>RR ratio CI LB</i>		0.89	0.96	0.96
Sensitivity	61%	73%	68%	73%
<i>RR ratio CI LB</i>		1.08	1.01	1.09
Specificity	76%	55%	72%	66%
<i>RR ratio CI LB</i>		0.62	0.84	0.76

Efficacy Summary

- Accuracy non-inferiority in both studies
- **Specificity non-inferiority in Study 32**
(market applicable population)
- **Sensitivity non-inferiority in Study 33**
(patients already determined to need coronary angiography)
- Variable SPECT comparator performance characteristics between studies 32 & 33

Studies	32	33
SPECT Sensitivity	78%	61%
SPECT Specificity	64%	76%

Safety

- **AI-700 Exposure**
 - **1,194 patients & healthy volunteers**
 - **911 phase 3 safety database**
- **Serious adverse events**
- **Events prompting AI-700 discontinuation**

Design Safety Limitations

Study Procedures

Rest

**AI-700
ECHO**



≥ 60
min

Dipyridamole



~ 3 min

Stress

**AI-700
ECHO**

11 Serious Adverse Events

Patients	Key events	Post Dose
3	Syncope/bradycardia/hypotension (2)	1st
2	Myocardial infarction	2nd
1	Vertigo/hypertension	1st
1	Lethargy/mental status change	2nd
1	Eye pain/blurred vision	2nd
1	Fever, chills, flushing	2nd
1	Bronchospasm	2nd
1	Chest pain	2nd

Events Causing AI-700 Discontinuation

- **17 subjects had AI-700 permanently discontinued**
- **14 during/after first dose**
- **Variable acute symptoms:**
 - **Hypotension (7)**
 - **Syncope (3)**
 - **Rigors (2)**
 - **Other: weakness, flushing, dizziness, nausea**
- **7 subjects required AI-700 temporary interruption or dose adjustment**

Pattern of Events

72 year old female with history of angina and prior MI

- Flushing and dizziness within one minute of AI-700 initiation**
- “near syncope”**
- Junctional cardiac rhythm, HR 39
BP not measurable**
- Atropine/symptoms resolved/hospitalized**

Non-serious Adverse Events Prior to Dipyridamole Phase 3 Safety Database

<i>Event</i>	Patients n = 911
Headache	3%
Flushing	2%
Hypotension	1%
Rigors	1%
Dizziness	1%

Events occurring at $\geq 1\%$

Non-serious Adverse Events

Any-time Phase 3 Safety Database

<i>Event</i>	Patients n = 911
Headache	35%
Chest pain	11%
Nausea	10%
Flushing	9%
Chest discomfort	8%
Leukocytosis	7%
Dizziness	6%
Increased neutrophils	6%
"Feeling hot"	5%

Events occurring at $\geq 5\%$

Summary

- **Exploratory studies:**
 - **Signals for inflammatory events**
 - **Unclear delineation of “added value” of contrast to non-contrast echo**
- **Phase 3 studies:**
 - **Equivocal diagnostic efficacy**
 - **No delineation of “added value” of contrast to non-contrast echo**
 - **Safety signals for cardiovascular reactions**