PHASE II CLINICAL EVALUATIONS

The phase II clinical evaluations consists of three studies involving 60 subjects and 382 patients.

A summarization of the data to be reported is presented in Table I.

Table I
Phase II Clinical Investigations

Investigator	Type Study	Route of Admin.	Total Subj.(S)/ Pts.(P)	No. on HALDOL	No. on Placebo
A) Ballinger, C.	Open	Oral-Parenteral*	60(S)	43	17+
B) Tornetta, F.	D-B	I.M.	357(P)	258	99
C) Ferrari, H.	Open	I.V.	25(P)	25	--

*Both I.M. and I.V. Routes Used +Apomorphine only

A. Ballinger, C.M., M.D. (1)
Antiemetic effectiveness of HALDOL in subjects administered apomorphine.

Sixty institutionalized healthy male subjects, taking no other medications, were administered standardized doses of apomorphine to induce vomiting.

The objective of the study was to determine the effectiveness of prophylactic HALDOL in oral (as tablets, concentrate and sublingual*) dosage forms and parenteral dosage forms, the latter administered intravenously and intramuscularly, in protecting subjects against emetic doses of apomorphine. Parenteral HALDOL was compared with three other marketed antiemetic agents,

*SOLUTABS®-NDA 17-079

prochlorperazine, perphenazine, and trimethobenzamide for effectiveness in blocking apomorphine-induced vomiting. This study was also designed to determine the duration of action of HALDOL administered parenterally and orally.

Orally administered HALDOL was effective in almost all subjects when given in a dose of 0.06 mg/kg, one to two hours prior to apomorphine administration. The duration of action was about 18 hours.

As would be expected, the parenteral form of HALDOL was found to be significantly more potent than the oral dosage forms. An intramuscular dose of 0.007 mg/kg, about one-tenth the oral dose, was effective in all subjects tested. Premedication with 0.015 mg/kg of HALDOL intramuscularly was effective in all of 18 patients challenged with apomorphine 12 hours after administration.

Of the 43 subjects administered HALDOL, 25 received also other known antiemetics for comparative purposes.

In this study, the recommended intramuscular dose of prochlorperazine, 0.1 mg/kg, was effective in all subjects. When reduced by one-half (to 0.05 mg/kg), only 60% of the subjects were protected.

Perphenazine, even in doses one-fourth of that recommended, was 100% effective, but had a high incidence of unpleasant side effects and was generally tolerated poorly by the subjects.

Trimethobenzamide, at the recommended dose, was effective in only 50% of the subjects tested.

The investigator reported that side effects following HALDOL were less than those seen with prochlorperazine.

The investigator reported further that at the ED_{80} for HALDOL (0.007 mg/kg) administered I.M. to 12 volunteers, only one complained of any side effects; he reported only mild dizziness or jitteriness. Further, the investigator reported that at equipotent doses, prochlorperazine produced significant drowsiness in 2 of 7 subjects tested but HALDOL produced no drowsiness.

There was little discomfort associated with the intramuscular injection of HALDOL while 4 of 6 subjects complained of the discomfort with intramuscular perphenazine.

In conclusion, the investigator stated that HALDOL appears to be as effective as the presently used antiemetic medications and has the advantage of fewer unpleasant side effects; no allergic, hepatic, hematologic, or renal complications were noted.

B. Tornetta, F., M.D. (2)
A double-blind dose range evaluation of the antiemetic effectiveness of parenteral HALDOL in postoperative patients

A total of 357 female patients hospitalized for dilatation and curettage (D&C) were randomly placed in five groups receiving either HALDOL (0.25, 0.5, 1, 2, or 4 mg) intramuscularly or placebo.

Three doses of HALDOL (0.5, 1, or 2 mg) and placebo were studied in the first part of the investigation, and two doses of HALDOL (0.25 and 4 mg) and placebo were studied in the second part of the investigation.

The patient characteristics of the two study groups are presented in Table II-A and II-B.

Table II-A
Patient Characteristics

Drug Dose Group	No. of Pts.	Age		Weight	
		Mean	Range	Mean	Range
HALDOL 2 mg	52	37	19-55	133	77-200
HALDOL 1 mg	52	37	17-75	138	94-176
HALDOL 0.5 mg	53	38	18-80	135	94-189
Placebo	48	41	20-72	144	93-274

Table II-B
Patient Characteristics

Drug Group	Number of Patients	Age		Weight	
		Mean	Range	Mean	Range
HALDOL 4.0 mg.	51	37.5	19-77	140.0	91-236
HALDOL 0.25 mg.	50	34.8	18-59	141.9	94-225
Placebo	51	40.0	19-74	146.9	103-295

The drugs that are normally used for premedication in D&C procedures were similar in all test groups in both parts of the investigation. These drugs consisted primarily of meperidine, and atropine or scopolamine. Anesthesia was induced with sodium methohexital and cyclopropane. In most cases succinylcholine was used as a relaxant.

HALDOL or placebo (saline injection) was intramuscularly administered about 45 minutes after premedication and prior to induction.

At all dose levels, HALDOL reduced the incidence of postoperative nausea and vomiting.

For nausea, patients receiving HALDOL at doses 0.5 to 4.0 mg had a reduced incidence that was significantly different ($P < .01$) from the placebo control group.

For vomiting, in the groups receiving 0.5 mg or more of HALDOL the incidence was reduced significantly ($P < .02$ and in certain instances to $P < .01$) in comparison with that of the placebo groups.

Tables III-A and III-B show the occurrence of nausea and vomiting in each group studied.

Table III-A
Occurrence of Nausea or Vomiting

Drug Dose Group	NAUSEA					VOMITING		
	No. of Pts.	No. of Occur.	Severity*			No. of Pts.	No. of Occur.	Prochlorperazine Injection**
			1	2	3			
HALDOL 2.0 mg	3	4	2	2	-	6	6	2
HALDOL 1.0 mg	8	10	4	3	3	6	8	3
HALDOL 0.5 mg	8	10	6	4	0	4	7	2
Placebo	18	33	5	18	10	16	27	6

*Severity Code: 1-Mild, 2-Moderate, 3-Marked
**Number of patients who received Prochlorperazine for nausea

Table III-B
Occurrence of Nausea or Vomiting

Drug Group	Nausea					Vomiting		Pro-chlor. Inj.**	Total Pts.
	No. of Pts.	No. of Occur.	Severity*			No. of Pts.	No. of Occur.		
			1	2	3				
HALDOL 4.0 mg.	4	4	2	2	0	2	2	0	51
HALDOL .25 mg.	9	13	3	5	5	10	16	3	50
Placebo	16	30	1	12	17	12	21	7	51

*Severity Code: 1-Mild, 2-Moderate, 3-Marked
**Number of patients who received Prochlorperazine for nausea and vomiting

The antiemetic effectiveness of HALDOL was also demonstrated by comparing the number of patients in the HALDOL medication groups with those in the placebo groups who required injections of prochlorperazine to stop uncontrolled vomiting. Of the patients requiring this additional therapy, 13% of the patients on placebo (99), but only 3% of the patients on HALDOL, 0.5 to 4.0 mg dose groups (210) needed this additional therapy. At

the highest dose of HALDOL, 4.0 mg, no prochlorperazine was required by any patient.

None of the effective doses of HALDOL had any significant effect on speed of emergence from anesthesia.

The patient's global response to therapy was evaluated by the investigator. Summaries of these evaluations are presented in Tables IV-A and IV-B.

Table IV-A
Global Response To Therapy

Drug Dose Group	Patients' Response					Total Pts..
	Marked	Moderate	Minimal	None	Worse	
HALDOL 2 mg	46	5	1	0	0	52
HALDOL 1 mg	43	4	4	1	0	52
HALDOL 0.5 mg	44	6	2	1	0	53
Placebo	26	7	4	9	2	48

Table IV-B
Global Response To Therapy

Drug Group	Patients' Response					Total Pts.
	Marked	Moderate	Minimal	None	Worse	
HALDOL 4.0 mg.	47	3	1	0	0	51
HALDOL .25 mg.	38	5	4	3	0	50
Placebo	33	1	9	7	1	51

Marked = No nausea, no vomiting
Moderate = No vomiting and up to minimal nausea or vomiting immediately after removal of anesthetic mask
Minimal = Vomiting one or two times occurring four to six hours post-op. with moderate to severe nausea
None = Vomiting three or more times four to six hours post-op. with severe nausea

The effectiveness of HALDOL (doses of 0.5 to 4.0 mg) was significantly superior ($P < .05$ and in certain instances to $P < .01$) to that of placebo. The effectiveness was based upon comparison in which "Marked to Moderate" responses were combined, and "Minimal, None, and Worse" responses were combined.

Vital signs of the patients in the groups studied were not significantly altered by drug treatment.

Only a few mild adverse reactions could be attributed to HALDOL. Table V summarizes the side effects noted in the various test groups.

Table V
Side Effects

	HALDOL (dose)					
Side Effect	0.25mg	0.5mg	1.0mg	2.0mg	4.0mg	Placebo
Bradycardia				2	2	
Mild EPS-Puckering of Lips					1	
Restlessness					1	
Increased Blood Pressure					1	
Chills & Shivering	1					1
Increased Temp.						1
Blurred Vision						1
Total S.E.	1	0	0	2	5	3
Total Pts.with S.E.	1	0	0	2	5	2

The investigator concluded that HALDOL, administered preoperatively, effectively reduced postoperative nausea and vomiting in women undergoing D&C operations.

In summary, the effect of HALDOL administered prophylactically in reducing vomiting is illustrated by the fact that in the study of HALDOL administered at doses of 0.5, 1 and 2 mg, 24% of the placebo patients, but only 9% of the HALDOL-treated patients vomited postoperatively. In the second study, HALDOL administered at doses of 0.25 and 4 mg, 33% of the placebo patients but only 20% of the patients administered 0.25 mg and 4% of the patients administered 4 mg of HALDOL vomited postoperatively. Similar beneficial results with HALDOL were observed in measurements of postoperative nausea.

C. Ferrari, H., M.D. (3)
An open dose range evaluation of the antiemetic effectiveness of parenteral HALDOL in postoperative patients.

Twenty-five patients hospitalized for a variety of surgical procedures were placed in four groups to receive HALDOL intravenously (0.5, 1, 2, and 4 mg). HALDOL was administered therapeutically for the treatment of postoperative nausea and vomiting.

The patient characteristics of the four dose groups are presented in Table VI.

Table VI
Patient Characteristics

Dose Group HALDOL	No. of Pts.	Age		Sex		Weight	
		Mean	Range	Male	Female	Mean	Range
0.5 mg	8	34.6	17-60	1	7	134.4	117-156
1.0 mg	9	39.8	25-53	0	9	137.4	114-160
2.0 mg	6	37.2	22-48	1	5	133.5	115-150
4.0 mg	2	42.0	38-46	1	1	150.0	116-184

HALDOL was administered in the recovery room after vomiting was observed.

The frequency of vomiting and nausea after the drug had been administered is presented in Table VII.

Table VII
Frequency of Vomiting and Nausea

HALDOL	No. Pts. In Study	Vomiting		Nausea	
		No. Pts.	Times	No. Pts.	Times
0.5 mg	8	1	1	4	5
1.0 mg	9	2	3	6	8
2.0 mg	6	0	0	2	2
4.0 mg	2	0	0	1	1

The investigator reported the global evaluation of the drug effect (Table VIII).

Table VIII
Global Evaluation

Drug Group HALDOL	Marked	Moderate	Minimal	None	Worse	Total Patients
0.5 mg	5	2	1	0	0	8
1.0 mg	7	2	0	0	0	9
2.0 mg	6	0	0	0	0	6
4.0 mg	2	0	0	0	0	2

In the global evaluation, all patients receiving 1.0 mg or greater of HALDOL experienced a marked to moderate response.

The sample size in this study is too small for statistical analysis of between dose group differences; however, the investigator stated that HALDOL administered at 1.0 to 2.0 mg was markedly effective in reducing the incidence of nausea and vomiting when given therapeutically.

No remarkable changes in vital signs occurred during the study period.

Side effects following HALDOL were in general mild, and the following were noted: five cases of prolonged recovery from anesthesia, one at 1.0 mg, three at 2.0 mg, and one at 4.0 mg; eight cases of restlessness, three at 0.5 mg, four at 1.0 mg, and one at 2.0 mg; one case of hypotension and lethargy at 0.5 mg (this patient is also listed above as showing restlessness); one case of increased muscle tone at 1.0 mg (this patient is also listed above as showing restlessness).