2.3 SUMMARY OF INDIVIDUAL CLINICAL TRIAL IN ACNE

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2.3.1 Type of Trial

A double-blind randomised trial to compare efficacy and safety of two retinoids, ROACCUTANE (isotretinoin) and TIGASON (etretinate), in patients with cystic acne.

The effects of each retinoid on quantity and quality of forehead sebum production were compared and correlated with the clinical response.

2.3.2 Demography, Criteria for Inclusion and Exclusion, Duration of Disease, Prior Treatment

Demography

The number of patients, their sex, age and duration of cystic acne are shown in Table 1.

TABLE 1

Demography of Patients in Trial

	ROACCUTANE	TIGASON
Number of Patients	10	10
Male	10	10
Female	0	0
Mean age (yrs)	21.2	27.8
Range	[redacted]	
±SD	3.6	11.7
Mean Duration of Disease (yrs)	6.8	10.1
Range	3.0 - 11.0	4.3 - 15.1

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The age range for the whole population was [redacted] except for two patients, ages [redacted] and [redacted] years, who were both randomly selected to the TIGASON group. This skew in the ages of the TIGASON group was also reflected in the longer mean duration of disease in that group.

Inclusion Criteria

1. All patients had cystic acne defined as the presence of ten or more cysts, measuring 4 mm or more in diameter, on the face, back or chest.
   Patients may have had fewer than ten cysts if the sum of the greatest diameters of the lesions is greater than or equal to 50 mm.

2. All patients were between 18 - 40 years of age.
3. All patients were in good general health.

Exclusion Criteria

1. All women were excluded.
2. Impaired renal function.
3. Impaired hepatic function.
4. Any pre-existing condition which may be exacebated by the superimposition of symptoms of hypervitaminosis A.
5. Dietary variation resulting in excessive intake (greater than 50,000 u/day of Vitamin A).

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Prior Treatment

Before entry into the trial all the patients with the exception of patient [redacted] had been treated with a variety of 'conventional' therapies: antibiotics (oral and topical), steroids (oral, topical and intralesional), ultraviolet light, topical retinoic acid, surgical drainage, oral vitamin A, liquid nitrogen, dry ice, oral zinc and dermabrasion. Response to these treatments was generally unsatisfactory or at best only suppressive. The following proscriptions applied where necessary:

a) Ultraviolet light and sun bathing was stopped one week prior to entry.
b) Topical therapy was stopped two weeks prior to entry.
c) Systemic therapy was stopped four weeks prior to entry.

Thus many patients were in a worsening phase of the disease at entry.

2.3.3 Number of Patients Receiving ROACCUTANE/TIGASON, Number and Reasons for Interruption of Therapy, Deviations from Protocol

There were 10 patients in both the ROACCUTANE and the TIGASON group.

There were no interruptions of therapy.

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Deviations from Protocol

Patient [redacted] restarted coded medication (TIGASON) after only two weeks in the follow-up period.

Patient [redacted] increased his coded medication (TIGASON) to 1.5mg/kg/day at 6.5 weeks and continued at this dose for the remaining 1.5 weeks. Ten days into the follow-up, the patient started open treatment with ROACCUTANE.

Patient [redacted] was [redacted] years of age on entry to the study, a minimum of 18 years is required by the protocol.

Patients [redacted] and [redacted] were [redacted] years at entry.

2.3.4 Daily Dosage

The approximate daily dosage of either retinoid was 1.0mg/kg/daily.

Table 2 shows the actual mean daily dosage and range and the actual mg/kg daily dose.

TABLE 2

Mean Daily Dosage; mg and mg/kg

	ROACCUTANE	TIGASON
Mean	82.0	81.0
Range	60 - 100	60 - 130
mg/kg	1.04	1.00
±SE	0.0	0.1

2.3.5 Duration of Dosage

The duration of therapy for both regimes was eight weeks.

2.3.6 Nature of Treatment of Control Group

This was a comparative trial of two retinoids in cystic acne. The control group received TIGASON in the same 1mg/kg/day dosage as the ROACCUTANE group, as shown in 2.3.4. The patients were randomly selected to either treatment and only at the end of the eight-week off-drug follow-up period was the randomisation code broken.

2.3.7 Results - Efficacy

1. Evaluation of Response

a) Objective score

The patients were examined at baseline and at monthly intervals during treatment.

The cystic lesions were counted on the face (including under the mandible), the back (including back of neck, shoulders and upper arms) and the chest (including anterior neck and supraclavicular areas.

b) Subjective score

Patients and physicians global evaluation

At the completion of treatment both the patient and the physician made a global assessment of the results of therapy relative to baseline according to the key:-

definitely worse	-2
probably worse	-1
no change	0
probably better	+1
definitely better	+2
almost clear	+3
totally clear	+4

c) Sebum production Collections of forehead sebum were obtained before, during and after treatment according to the standard quantitative procedure of Strauss and Pochi[1].

2. Results of comparative trial

Cyst count

Total Cyst Count

Table 3 shows the mean total cyst count before, during and after eight weeks' treatment.

Reference

1. Strauss J S and Pochi P, J Invest Dermatol, 1961, 36: 293-298.

TABLE 3

Mean total cyst count

Weeks	ROACCUTANE Cysts	% Change	No. Pts	TIGASON Cysts	% Change	No. Pts	p‡
Baseline	38.9 ± 5.8		10	38.8 ± 6.9		10	
2 weeks	29.8 ± 4.9	-23*	10	29.3 ± 4.9	-24*	10	0.524
4 weeks	18.2 ± 2.8	-53*	10	26.9 ± 5.3	-30*	10	0.121
8 weeks	12.4 ± 3.6	-68*	10	26.2 ± 6.1	-32	10	0.08
4 weeks off drug	13.4 ± 4.2	-66*	10	25.5 ± 6.6	-34	10	0.129
8 weeks off drug	15.3 ± 5.5	-61*	10	27.3 ± 4.4	-26	10	0.093

* $p < 0.05$, significant change from baseline, within group.

‡ Two-sample t-test comparison of treatment changes

At 2, 4, and 8 weeks on drug and 4 and 8 weeks off drug there was a statistically significant change from baseline within the ROACCUTANE group in the total cyst count.

In the TIGASON group there was a statistically significant change from baseline only at 2 and 4 weeks of therapy.

Although at 8 weeks the decrease in number of cysts in the ROACCUTANE group was 68%, as opposed to 31% in the TIGASON group, this difference was not statistically significant.

Cyst Count - Face

Table 4 shows the mean facial cyst count

TABLE 4

Mean facial cyst count

Week	ROACCUTANE			TIGASON			
	Cysts	% Change	No. Pts	Cysts	% Change	No. Pts	p‡
Baseline	9.4		10	9.7		10	
±	2.1			2.1			
2 weeks	6.3	-33*	10	7.8	-20	10	0.305
±	1.3			1.6			
4 weeks	3.6	-62*	10	5.6	-42	10	0.254
±	0.9			1.1			
8 weeks	0.7	-93*	10	6.7	-30	10	0.012
±	0.3			1.7			
4 weeks off drug	1.5	-84*	10	7.1	-26	10	0.045
±	0.5			1.8			
8 weeks off drug	4.1	-56	7	8.4	+13	7	0.039
±	2.7			1.7			

* $p < 0.05$ one-sided comparison with baseline

‡ Two-sample t-test comparison of treatment changes

At eight weeks on treatment, four weeks off drug and eight weeks off drug there was a statistically significant difference between ROACCUTANE and TIGASON for the mean change from baseline of facial cystic lesions, with ROACCUTANE giving the better results.

Cyst Count - Back and Chest

Similar results, although not statistically significant, occurred with other skin areas.

Table 5 shows the change in mean number of cysts in all areas at eight weeks.

TABLE 5

Change in mean number of cysts at eight weeks

Area	ROACCUTANE	% Change	No. Pts	TIGASON	% Change	No. Pts	p‡
Total ±	-26.5* 4.6	-68	10	-12.6 8.2	-32	10	0.080
Face ±	-8.7* 2.0	-93	10	-3.0 2.4	-31	10	0.042
Chest ±	-9.1* 2.5	-67	10	-2.9 4.1	-28	10	0.109
Back ±	-8.7* 2.2	-55	10	-6.7 3.9	-36	10	0.330

* statistically significant $p < 0.05$ change from baseline

‡ Two-sample t-test comparison of treatment changes

Patients' and Physician's Global Evaluations

Table 6 shows the mean subjective scores at eight weeks from baseline in both groups of patients, as assessed by the physician.

TABLE 6

Mean Subjective Score Physician's Global Evaluation

	ROACCUTANE			TIGASON			
Week	Score	±SE	No. Pts	Score	±SE	No. Pts	p*
8	1.80	0.20	10	0.60	0.37	10	0.007
4 weeks off drug	1.20	0.39	10	0.50	0.50	8	0.144

* one-sided probability

key:-		
	definitely worse	-2
	probably worse	-1
	no change	0
	probably better	+1
	definitely better	+2
	almost clear	+3
	totally clear	+4

Patients treated with ROACCUTANE achieved at eight weeks a minimal - definite improvement score whereas TIGASON patient showed no change.

This difference between the two groups is statistically significant.

Table 7 shows a similar result in the patients' own assessment of their response.

TABLE 7

Mean Subjective Score Patients Global Evaluation

	ROACCUTANE			TIGASON			
Week	Score	±SE	No. Pts	Score	±SE	No. Pts	p*
8	1.70	0.15	10	0.60	0.34	10	0.006
4 weeks off drug	1.00	0.36	10	0.38	0.46	8	0.153

* one-sided probability

Key:

definitely worse	-2
probably worse	-1
no change	0
probably better	+1
definitely better	+2
almost clear	+3
totally clear	+4

Using this evaluation procedure, patients treated with ROACCUTANE showed an improvement at eight weeks which was significantly better than that on TIGASON.

Table 8 shows the distribution of patients at eight weeks and at four weeks in the two groups off drug who achieved the status of definitely worse (-2), no change (-1, 0, +1) or definitely or markedly improved (+2 or more), as assessed by the physician.

TABLE 8

Number of patients achieving levels of improvement

	ROACCUTANE			TIGASON		
Week	Worse	No Change	Better	Worse	No Change	Better
8	0	3	7	1	7**	2
4 weeks* off drug	1	4	5	1	5	2

* compared to end of therapy

** probability of this distribution of response is = 0.01

The majority of patients treated with ROACCUTANE showed 'marked improvement' whereas those patients treated with TIGASON showed 'no change' at eight weeks.

There was little change in status of the disease at four weeks after discontinuation of therapy compared to the evaluation at the end of therapy.

Sebum production

The mean sebum production during the trial and the follow-up period is shown in Table 9.

TABLE 9

Mean Sebum Production (mg/100cm^2/3hr)

	ROACCUTANE			TIGASON			
Week	Sebum	% Change	No. Pts	Sebum	% Change	No. Pts	p‡
Baseline	2.56 ± 0.44		10	3.61 ± 0.99		10	
2 weeks	1.34 ± 0.31	-48*	10	1.94 ± 0.50	-47	9	0.638
4 weeks	0.42 ± 0.06	-83*	10	1.65 ± 0.28	-54*	10	0.439
8 weeks	0.33 ± 0.07	-87*	10	1.75 ± 0.37	-52	10	0.385
4 weeks off drug	0.71 ± 0.14	-72*	10	1.04 ± 0.32	-75*	7	0.778
8 weeks off drug	1.27 ± 0.25	-50*	9	1.88 ± 0.18	-52	7	0.717

* $p < 0.05$ change from baseline

There was a greater reduction of sebum production in the ROACCUTANE group than in the TIGASON group. At all assessment points there was a statistically significant change from baseline within the ROACCUTANE group, whereas this was seen only at Week 4 during, and Week 4 after treatment within the TIGASON group.

However at no time was there a statistically significantly greater fall in sebum production on either retinoid.

2.3.8 Adverse Reactions

Clinical

All symptoms and signs were graded according to severity as mild, moderate or severe. All symptoms or signs which increased their severity by at least one grade whilst on drug were considered to be probable adverse experiences.

Symptoms that began on drug therapy and did not change their severity grading were considered possibly drug related. Symptoms, exception of hair loss, that developed after drug therapy was discontinued were considered to be remotely drug related.

The incidences of all possible adverse experiences are shown for the two groups in Table 10.

TABLE 10

Incidence of adverse events on ROACCUTANE and TIGASON

	ROACCUTANE		TIGASON	
Organ System	No Pts	%	No Pts	%
Integumentary	**10**	**100**	**10**	**100**
Rash	1	10	2	20
Pruritus	7	70	5	50
Sunburn	3	30	2	20
Dry Skin	9	90	8	80
Peeling	1	10	6	60
Finger tip peeling	2	20	5	50
Cheilitis	9	90	8	80
Fragility of skin	1	10	3	30
Facial dermatitis	4	40	4	40
Hair loss	4	40	6	60
Respiratory	**7**	**70**	**4**	**40**
Dry nose	7	70	5	50
Epistaxis	3	30	3	30
Musculo-skeletal	**3**	**30**	**1**	**10**
Joint pain	3	30	1	10
Muscle cramp	1	10		
Gastro-intestinal	**7**	**70**	**4**	**40**
Soreness of mouth	4	40	2	20
Nausea	1	10		
Increased appetite	2	20		
Anorexia			1	10
Thirst	4	40	3	30
Abdominal pain	1	10	1	10
Central nervous system	**2**	**20**	**3**	**30**
Headache	1	10	1	10
Insomnia	1	10	2	20
Special sensory	**4**	**40**	**3**	**30**
Diploplia			1	10
Pain in the eyes	1	10	1	10
Irritation of the eyes	3	30	2	20
Miscellaneous	**4**	**40**	**1**	**10**
Lethargy	4	40	1	10
Fever			1	10
Number of patients with adverse experiences	10	100	10	100

All patients in both treatment groups were affected by minor and clinically inconsequential symptoms. Cheilitis and dry skin affected 90% of patients on ROACCUTANE and 80% of patients on TIGASON.

There were no marked differences in side-effects of side effects of these two retinoids.

In no case were these symptoms regarded as other than mild and in no instance was the dosage of retinoid reduced or a patient removed from the study due to a drug-related adverse event.

Laboratory investigations

Data obtained

The following routine blood and urine studies were obtained at baseline, weeks 1, 2 and 8. FBC, WBC, differential, reticulocytes, platelets, haematocrit, complete urine analysis, fasting blood sugar, BUN and serum creatinine, serum albumin and total protein, serum bilirubin, SGOT, SGPT, alkaline phosphatase and LDH, cholesterol and triglycerides.

Assignation as a drug effect

Values outside the normal range of the laboratory were assigned in a 'blind' manner as remotely, possibly or probably related to the test medications according to guidelines in the protocol.

As the retinoids are new chemical entities and their effect on laboratory parameters could not be predicted, essentially all abnormalities were classified as at least possible unless they could be clearly categorised as remote. Thus many inconsequential laboratory abnormalities are included in the tables.

Table 11 shows the number and percentage of patients who had laboratory abnormalities classified as probably or possibly drug related.

TABLE 11

Number of patients and percentage with laboratory abnormalities

Organ System - high or low value		ROACCUTANE No Pts	%	TIGASON No Pts	%
Haematologic		**3**	**30**	**6**	**60**
Haematocrit	low			3	30
WBC	high	1	10		
Neutrophils	high	1	10	1	10
Monocytes	high	1	10	2	20
Basophils	high	1	10	2	20
Platelets	low			2	20
Hepatic		**8**	**80**	**2**	**20**
SGOT	high	3	30	2	20
Bilirubin	high	1	10		
Cholesterol	high	2	20		
Total protein	low	1	10		
Albumin	high	3	30		
HDL	low	1	10		
SGPT	high			2	20
Miscellaneous chemistries		**2**	**20**	**2**	**20**
Triglycerides	high	2	20	2	20
Urinary		**6**	**60**	**4**	**40**
wbc in urine/hpf	high	3	30	3	30
wbc in urine	high	1	10		
Bacteria in urine		4	40	3	30
Number of patients with adverse experiences		10	100	9	90

The recorded abnormalities including single isolated abnormalities that may be of clinical relevance are discussed below.

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ROACCUTANE

The following had isolated abnormalities at eight weeks:-

Patient [redacted] had 210 basophils/cmm.
Patient [redacted] had an elevation of triglycerides to 210mg/dl.
Patient [redacted] an elevation of bilirubin to 1.1mg/dl.
Patient [redacted] had 1139 monocytes/cmm and an elevation of triglycerides to 193mg/dl.
Patient [redacted] had a decreased HDL level to 28mg/dl and an increased neutrophil count (8610/cm).

Except for the triglyceride not one of these abnormalities was commented upon by the investigator.

TIGASON

The following isolated abnormalities were seen at eight weeks:-

Patient [redacted] had 938 lymphocytes/cmm and 696,000 platelets/cmm on 1.5mg/kg/day.
Patient [redacted] had a decreased haematocrit of 34%.
Patient [redacted] had basophil count 212/cmm, an SGOT level 45units, an SGPT level 128units and an elevated triglyceride 208mg/dl.

Patient [redacted] had 7875 neutrophils, 945 monocytes, 210 basophils/cmm and a persistent decrease in platelets 169,000/cmm.

Patient [redacted] had elevated levels of SGOT (60 units) and SGPT (94 units).

Patient [redacted] had 1200 monocytes/cmm.

Patient [redacted] had 804,000 platelets. The investigator noted that this could have been a laboratory error.

Except for the liver transaminases (patients [redacted] and [redacted]), none of the abnormalities caused the investigator to comment.

Special tests

Ophthalmologic examination

Ten patients complained of symptoms. In eight the complaint was of slight conjunctival irritation.

Patient [redacted] was noted to have mild follicular hyperplasia and an area of 'increased pigment'. Patient [redacted] had pigmentation of the disc which apparently was not present at baseline.

Semen analyses

There were no differences in either group between baseline and at end of therapy in the following parameters: volume, sperm count, % mobility, wbc/hpf.

2.3.9 Conclusion and Comment

This study demonstrates that both retinoids at 1.0mg/kg/day are effective and safe treatments of cystic acne. However, ROACCUTANE is statistically significantly superior to TIGASON on treating facial acne, but the superiority did not reach statistical significance for total acne counts (ie face, chest and back). The incidence and spectrum of clinical and laboratory adverse reactions were similar with both retinoids. The mucocutaneous clinical symptoms were well tolerated by the patients and the laboratory abnormalities were not sufficient to lead to interruption of therapy.

The reduction in sebum production associated with ROACCUTANE during therapy parallelled the clinical improvement.

The reduction of sebum production was less in the TIGASON group, but more marked than has been seen in other studies.

2.3 SUMMARY OF INDIVIDUAL CLINICAL TRIAL

Redacted under Section 40 of the FOIA.

2.3.1 Type of Trial

A stratified randomised double-blind comparison of two different treatment schedules of ROACCUTANE in cystic acne.

The two stratifications were:-

predominantly facial lesions (Group I)

and predominantly truncal lesions (Group II)

The two treatment schedules were:-

either a two-week or a four-week loading dose. The loading and maintenance doses in Group I were one half of the loading and maintenance doses in Group II, (see 2.3.4).

2.3.2 Demography, Criteria for Inclusion and Exclusion, Duration of Disease, Prior Treatment

Demography

The number of patients, their sex, age and duration of cystic acne are shown in Table 1.

TABLE 1

Demography of Patients in Trial

Group I - Predominantly facial lesions

	Two-week Loading Dose	Four-week Loading Dose
Number of Patients	10	10
Male	5	7
Female	5	3
Mean age (yrs)	23.3	21.8
Range	[redacted]	
Mean Duration of Disease (yrs)	8.9	5.7
Range	5.3 - 22.7	1.7 - 12.3

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Group II - Predominantly truncal lesions

	Two-week Loading Dose	Four-week Loading Dose
Number of Patients	10	10
Male	10	10
Female	0	0
Mean age (yrs)	19.8	20.9
Range	[redacted]	
Mean Duration of Disease (yrs)	6.7	7.8
Range	3.3 - 14.9	3.2 - 22.3

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Inclusion Criteria

1. 40 patients with cystic acne defined by the presence of ten or more cysts, 4 mm or more in longest diameter. Patients with fewer than ten cysts could be entered only if the sum of the greatest diameters of their lesions was greater than or equal to 50 mm. Patients entered were stratified into two groups:

   Group I 20 patients with predominantly facial lesions (> 60% lesions on the face)

   Group II 20 patients with predominantly truncal lesions (> 60% lesions on or below the neck)

   Within each of these two stratifications, patients were randomly assigned to one of two different treatment schedules (10 patients in each schedule).

2. All patients were between 18 - 40 years of age.

3. All patients were in good general health.

Exclusion Criteria

1. Impaired renal function.
2. Impaired hepatic function.
3. Impaired neurologic function.
4. Impaired haematologic function.
5. Ultraviolet light therapy.
6. Topical therapy except that 1% hydrocortisone ointment was permitted as adjunctive therapy for cutaneous scale effects of ROACCUTANE.
7. Dietary excess of Vitamin A.
8. A pre-existing condition which might be exacerbated by the superimposition of symptoms of hypervitaminosis A.

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Prior Treatment

Before entry into the trial all the patients with the exception of patient [redacted] had been treated with a variety of 'conventional' therapies: antibiotics (oral and topical), steroids (oral, topical and intralesional), ultraviolet light, topical retinoic acid, surgical drainage, oral vitamin A, liquid nitrogen, dry ice, oral zinc and dermabrasion. Response to these treatments was generally unsatisfactory or at best only suppressive. The following proscriptions applied where necessary:

a) Ultraviolet light and sunbathing were stopped one week prior to entry.

b) Topical therapy was stopped two weeks prior to entry.

c) Systemic therapy was stopped four weeks prior to entry.

Thus many patients were in a worsening phase of the disease at entry.

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2.3.3 Number of Patients Receiving ROACCUTANE, Number and Reasons for Interruption of Therapy, Deviations from Protocol

All 40 patients received ROACCUTANE.

In Group I, patient [redacted] who was assigned to receive the loading dose for four weeks, actually received the loading dose (1.0mg/kg/day) for six weeks.
In Group II, patient [redacted] who had been assigned to receive the loading dose (2.0mg/kg/day) for two weeks, actually only received it for one week.

Patient [redacted] received only 15 weeks therapy because [redacted] failed to pick up [redacted] medication for the last week of treatment.

None of these deviations were thought sufficient to affect the efficacy or safety analyses and these patients' data have been included in all analyses.

There were no interruptions of therapy.

2.3.4 Daily Dosage

The daily dosage differed for Group I and Group II patients.

Group I

The loading dose was 1.0mg/kg/day given for two or four weeks followed by a maintenance dose of 0.25mg/kg/day for the remainder of the 16 weeks.

Group II

The loading dose was 2.0mg/kg/day given for two or four weeks followed by a maintenance dose of 0.5mg/kg/day for the remainder of the 16 weeks.

The actual mean daily dosage, range and number of patients are shown in Tables 2 and 3.

TABLE 2

Group I - ROACCUTANE mg/day

	Two-Week Loading Dose	Four-Week Loading Dose
Mean dose	46.6	64.9
Range	30 - 160	30 - 160
Number of patients	10	10

TABLE 3

Group II - ROACCUTANE mg/day

	Two-Week Loading Dose	Four-Week Loading Dose
Mean dose	46.6	64.9
Range	30 - 160	30 - 160
Number of patients	10	10

2.3.5 Duration of Dosage

Tables 4 and 5 show the duration of dosage in days in the two groups.

TABLE 4

Duration of Dosage - Group I

	Two-Week Loading Dose	Four-Week Loading Dose
Mean	113.4	111.5
Range	112 - 116	91 - 121

TABLE 5

Duration of Dosage - Group II

	Two-Week Loading Dose	Four-Week Loading Dose
Mean	112.5	113.5
Range	110 - 117	108 - 119

2.3.6 Nature of Treatment of Control Group

This was a stratified, two-dosage comparative study with no comparator drug or placebo group.

2.3.7 Results - Efficacy

1. Evaluation of Response

a) Objective score

The patients were examined at baseline and at monthly intervals during treatment.

The cystic lesions were counted on the face (including under the mandible), the back (including back of neck, shoulders and upper arms) and the chest (including anterior neck and supraclavicular areas.

b) Subjective score

Patients' and physician's global evaluation

At the completion of treatment both the patient and the physician made a global assessment of the results of therapy relative to baseline according to the key:-

definitely worse	-2
probably worse	-1
no change	0
probably better	+1
definitely better	+2
almost clear	+3
totally clear	+4

In order to determine the optimal duration of the loading dose, a comparison of the two different treatment schedules can be made within each stratification (Group I and Group II) and across stratifications (combining Group I and Group II patients according to treatment schedule received).

Three comparisons were then made:

1) Comparison of responses to the two treatment schedules within Group I.
2) Comparison of the responses to the two treatment schedules within Group II.
3) Comparison of the responses of all patients receiving the two-week loading dose schedule (Group I and Group II combined) with that of all patients receiving the four-week loading dose schedule.

2. Comparison of responses to the two treatment schedules within Group I (patients with predominantly facial lesions).

Cyst count

Tables 6, 7 and 8 show the mean total cyst count before, during and after sixteen weeks treatment.

Table 6 shows the mean total cyst count in the two treatment schedules in Group I.

TABLE 6

Mean total cyst count +SE

	Two-Week Loading Dose	No.⊕ Pts	Four-Week Loading Dose	No. Pts	p‡
Baseline	22.7 ± 5.7	7	24.0 ± 3.2	10	0.401
Week 1	23.3 ± 4.0	8	25.3 ± 3.8	10	0.358
Week 2	26.4 ± 4.7	8	27.6 ± 3.9	10	0.422
Week 4	21.1 ± 3.5	8	23.3 ± 4.1	10	0.345
Week 8	14.6 ± 2.8	8	12.5* ± 2.6	10	0.707
Week 12	10.4* ± 5.1	8	10.2* ± 2.8	10	0.512
Week 16	7.5* ± 3.7	8	6.8* ± 2.2	10	0.564
4 weeks post-drug	3.3* ± 1.7	7	3.9* ± 1.8	8	0.409

* probability < 0.05, one-sided comparison with baseline, t-test.

‡ probability, two-sample t-test

⊕ two patients had less than 10 cysts at baseline and they were not evaluated by cyst count but were by global evaluation (see Table 10).

Table 7 shows the mean facial cyst count in the two treatment schedules in Group I

TABLE 7

Mean facial cyst count +SE

	Two-Weeks Loading Dose	No. Pts	Four-Weeks Loading Dose	No. Pts	p‡
Baseline	16.9 ± 3.3	7	19.9 ± 1.6	10	0.214
Week 1	16.3 ± 2.0	8	20.4 ± 2.9	10	0.127
Week 2	18.3 ± 1.8	8	22.4 ± 3.9	10	0.174
Week 4	11.8 ± 1.1	8	16.6 ± 3.0	10	0.080
Week 8	8.5 ± 1.6	8	8.7* ± 2.1	10	0.470
Week 12	5.1* ± 2.6	8	6.2* ± 1.5	10	0.366
Week 16	2.4* ± 1.1	8	3.4* ± 0.7	10	0.225
4 weeks post-drug	2.6* ± 1.8	7	1.9* ± 1.1	8	0.629

* probability <0.05, one-sided comparison with baseline, t-test

‡ probability, two-sample t-test

Table 8 shows the mean truncal cyst count in the two treatment schedules in Group I.

TABLE 8

Mean truncal cyst count +SE

	Two-Weeks Loading Dose	No. Pts	Four-Weeks Loading Dose	No. Pts	p‡
Baseline	5.9 ± 2.9	7	4.7 ± 2.3	10	0.642
Week 1	7.0 ± 2.7	8	4.9 ± 2.1	10	0.728
Week 2	8.1 ± 3.5	8	5.2 ± 1.9	10	0.761
Week 4	9.4 ± 3.1	8	6.7 ± 2.5	10	0.744
Week 8	6.1 ± 2.7	8	3.8 ± 1.8	10	0.759
Week 12	5.3 ± 3.6	8	4.0 ± 2.0	10	0.617
Week 16	5.1 ± 3.4	8	3.4 ± 1.7	10	0.667
4 weeks post-drug	0.7 ± 0.5	7	2.0 ± 1.4	8	0.208

* probability <0.05, one-sided comparison with baseline, t-test

‡ probability, two-sample t-test

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The missing baseline patient in the two-week loading dose schedule was patient [redacted] who did not have a true baseline evaluation.

Also missing in this schedule are patients [redacted] and [redacted] who were evaluated by measurement of the size of their lesions.

Table 9 shows the change in total size of longest diameters of the acne cysts in patients [redacted] and [redacted].

TABLE 9

Redacted under Section 40 of the FOIA.

	Patient [redacted]		Patient [redacted]	
	Change mm	%	Change mm	%
After 1 week	-8	-14.5	-35	-55.6
After 2 weeks	-16	-29.1	-43	-68.3
After 4 weeks	-16	-29.1	-43	-68.3
After 8 weeks	-24	-43.6	-63	-100
After 12 weeks	-41	-74.5	-63	-100
After 16 weeks	-55	-100	-63	-100
Four weeks post-drug	-50	-100	-58	-92.1

There were no statistically significant differences between the two treatment schedules at any of the evaluations.

Patients' and Physician's Global Evaluations

Table 10 shows the mean subjective scores at sixteen weeks from baseline in both groups of patients as assessed by the physician.

TABLE 10

Mean Subjective Score +SE Physicians Global Evaluation

	Two-Week Loading Dose	No. Pts	Four-Week Loading Dose	No. Pts	p
16 Weeks	2.2	10	2.5	10	0.649
4 Weeks Post-drug	2.2	10	2.9	7	0.790

TABLE 11

Mean Subjective Score +SE Patients' Global Evaluation

	Two-Week Loading Dose	No. Pts	Four-Week Loading Dose	No. Pts	p
16 Weeks	2.2	10	2.4	10	0.600
4 Weeks Post-drug	2.2	10	2.9	7	0.790

Key:

definitely worse	-2
probably worse	-1
no change	0
probably better	+1
definitely better	+2
almost clear	+3
totally clear	+4

There were no statistically significant differences between the treatment schedules and no marked diference between the way the physician rated the patients' improvement and the way the patient rated [redacted] own improvement.

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Table 12 shows the number of patients who responded with a "definite improvement" or better (> +2) and "almost clear" or better (> +4) on the physician's global evaluation for the two schedule groups.

TABLE 12

	Two-Week Loading Dose	Four-Week Loading Dose
No. responding with "definite improvement" or better	8 of 10	10 of 10
No. responding with "almost clear" or better	3 of 10	1 of 10

3. Comparison of the responses to the two treatment schedules within Group II (patients with predominantly truncal lesions)

Table 13 shows the mean total cyst count in the two treatment schedules in Group II.

TABLE 13

Mean total cyst count +SE

	Two-Week Loading Dose	No. Pts	Four-Week Loading Dose	No. Pts	p‡
Baseline	42.8 ± 4.6	10	42.6 ± 8.4	10	0.508
Week 1	43.0 ± 4.7	10	31.0 ± 6.4	9	0.924
Week 2	41.2 ± 3.1	10	38.1 ± 9.7	9	0.616
Week 4	29.8* ± 3.8	10	26.7* ± 3.5	10	0.722
Week 8	20.1* ± 3.3	10	20.1* ± 3.3	10	0.500
Week 12	14.8* ± 2.8	10	18.9* ± 3.6	10	0.190
Week 16	7.9* ± 1.6	10	14.9* ± 2.0	10	0.008
4 weeks post-drug	4.6* ± 2.0	9	9.0* ± 2.1	9	0.072

* probability < 0.05, one-sided comparison with baseline, t-test.

‡ probability, two-sample t-test

Table 14 shows the mean truncal cyst count in the two treatment schedules in Group II.

TABLE 14

Mean truncal cyst count +SE

	Two-Week Loading Dose	No. Pts	Four-Week Loading Dose	No. Pts	p‡
Baseline	32.4 ± 2.8	10	28.7 ± 5.1	10	0.734
Week 1	33.5 ± 3.5	10	21.1 ± 3.7	9	0.987
Week 2	30.8 ± 2.1	10	27.0 ± 6.9	9	0.695
Week 4	23.3* ± 2.4	10	19.5* ± 2.5	10	0.860
Week 8	16.8* ± 3.0	10	17.0* ± 3.4	10	0.482
Week 12	13.0* ± 2.4	10	16.3 ± 3.5	10	0.224
Week 16	7.1* ± 1.5	10	13.0* ± 2.1	10	0.018
4 weeks post-drug	4.1* ± 1.8	9	8.1* ± 1.9	9	0.075

* probability < 0.05, one-sided comparison with baseline, t-test.

‡ probability, two-sample t-test.

Table 15 shows the mean facial cyst count in the two treatment schedules in Group II.

TABLE 15

Mean facial cyst count +SE

	Two-Week Loading Dose	No. Pts	Four-Week Loading Dose	No. Pts	p‡
Baseline	10.4 ± 2.4	10	13.9 ± 3.9	10	0.229
Week 1	9.5 ± 2.2	10	9.9 ± 2.9	9	0.459
Week 2	10.4 ± 2.3	10	11.1 ± 3.1	9	0.427
Week 4	6.5* ± 2.4	10	7.2* ± 1.7	10	0.408
Week 8	3.3* ± 1.1	10	3.1* ± 1.0	10	0.553
Week 12	1.8* ± 0.8	10	2.6* ± 0.8	10	0.243
Week 16	0.8* ± 0.4	10	1.9* ± 0.7	10	0.107
4 weeks post-drug	0.4* ± 0.2	9	0.9* ± 0.6	9	0.242

* probability < 0.05, one-sided comparison with baseline, t-test.

‡ probability, two-sample t-test.

Although the mean total number of cysts and the mean number of cysts on the trunk were significantly less at 16 weeks for patients receiving the two-week loading dose, all other evaluations show no differences between the treatment groups.

Patients' and Physician's Global Evaluations

Table 16 shows the mean subjective scores at sixteen weeks from baseline in both groups of patients as assessed by the physician.

TABLE 16

Mean subjective score +SE Physician's Global Evaluation

	Two-Week Loading Dose	No. Pts	Four-Week Loading Dose	No. Pts	p
After 16 Weeks	2.4	10	1.7	10	0.041
4 weeks post-drug	2.1	10	2.2	9	0.585

TABLE 17

Mean subjective score +SE Patients' Global Evaluation

	Two-Week Loading Dose	No. Pts	Four-Week Loading Dose	No. Pts	p
After 16 Weeks	2.4	10	1.7	10	0.041
4 weeks post-drug	2.0	10	2.3	9	0.731

At 16 weeks there was a significantly better rating by both patients and physician in favour of the two-week loading dose. This result correlates with the lesion counts at this stage. However, at four weeks post-therapy there was no statistically significant difference between the two schedules.

Table 18 shows the number of patients who responded with a "definite improvement" or better (> +2) and "almost clear" or better (> +4) on the physician's global evaluation for the two schedule groups.

TABLE 18

	Two-Week Loading Dose	Four-Week Loading Dose
No. patients with "definite improvement" or better	10 of 10	8 of 10
No. patients with "almost clear" or better	0 of 10	0 of 10

After 16 weeks of treatment only one patient (No. [redacted]) was rated as having "no change" or "worsening".

4. Comparison of the response of all patients (Group I and Group II combined) receiving the two-week loading dose schedule with that of all patients receiving the four-week loading dose schedules.

Table 19 shows the mean change in cyst count in the two treatment schedules.

TABLE 19

Total

	Two-week loading dose			Four-week loading dose		
	Mean ±SE	% Change	No. Pts	Mean ±SE	% Change	No. Pts
Baseline	34.5 ± 4.2		7	33.5 ± 4.9		20
1 Week	34.2 ± 3.8	+1.4	18	28.0 ± 3.6	-7.8	19
2 Week	34.6 ± 3.2	-0.2	18	32.6 ± 5.0	-1.12	19
4 Week	25.9 ± 2.7	-25.4	18	25.0 ± 2.6	-25.4	20
8 Week	17.7 ± 2.3	-51.1	18	16.3 ± 2.2	-51.3	20
12 Week	12.8 ± 2.7	-67.8	18	14.6 ± 2.4	-56.6	20
16 Week	7.7 ± 1.8	-81.8	18	10.8 ± 1.7	-67.6	20
4 weeks post-drug	4.0 ± 1.3	-88.5	16	6.6 ± 1.5	-82.0	17

TABLE 20

Face

	Two-week loading dose			Four-week loading dose		
	Mean ±SE	% Change	No. Pts	Mean ±SE	% Change	No. Pts
Baseline	13.1 ± 2.1		17	16.9 ± 2.2		20
Week 1	12.5 ± 1.7	-5.0	18	15.4 ± 2.4	-0.7	19
Week 2	13.9 ± 1.7	+0.9	18	17.1 ± 2.8	+1.3	19
Week 4	8.8 ± 1.5	-34.2	18	11.9 ± 2.0	-29.6	20
Week 8	5.6 ± 1.1	-58.1	18	5.9 ± 1.3	-65.1	20
Week 12	3.3 ± 1.3	-78.8	18	4.4 ± 0.9	-74.0	20
Week 16	1.5 ± 0.6	-89.2	18	2.7 ± 0.5	-84.3	20
4 weeks post-drug	1.4 ± 0.8	-89.8	16	1.4 ± 0.6	-92.6	17

TABLE 21

Trunk

	Two-week loading dose			Four-week loading dose		
	Mean ±SE	% Change	No. Pts	Mean ±SE	% Change	No. Pts
Baseline	21.5 ± 3.8		17	16.6 ± 3.9		20
Week 1	21.7 ± 3.9	+5.2	18	12.6 ± 2.8	-15.3	19
Week 2	20.7 ± 3.3	-0.8	18	15.5 ± 4.2	-3.6	19
Week 4	17.1 ± 2.5	-20.0	18	13.1 ± 2.3	-21.1	20
Week 8	12.1 ± 2.4	-46.9	18	10.4 ± 2.4	-37.4	20
Week 12	9.6 ± 2.2	-61.1	18	10.2 ± 2.4	-38.9	20
Week 16	6.2 ± 1.7	-77.3	18	8.2 ± 1.7	-50.6	20
4 weeks post-drug	2.6 ± 1.1	-87.7	16	5.2 ± 1.4	-71.6	17

There was no real difference in the continuing improvement during therapy and at four weeks post-therapy between the two treatment regimes.

Patients' and Physician's Global Evaluations

TABLE 22

	Two-Week Loading Dose	Four-Week Loading Dose
Number of patients with > +2	18 of 20	18 of 20
Number of patients with > +4	3 of 20	1 of 20

Overall, after 16 weeks of therapy only three patients (Nos [redacted]) were rated as having "no change" in condition or "worsening".

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2.3.8 Adverse Reactions

Clinical

All symptoms and signs were graded according to severity as mild, moderate or severe. All symptoms or signs which increased in severity by at least one grade whilst on drug were considered to be a probable adverse experience.

Symptoms that began on drug therapy and did not change their severity grading were considered possibly drug-related.

Symptoms, with the exception of hair loss, that developed after drug therapy was discontinued were considered to be remotely drug-related.

The incidence of all possible adverse experiences are shown for the two groups in Tables 23 & 24.

Tables 23 & 24/

TABLE 23

Clinical Adverse Experiences Group I - facial acne

	Two-Week Loading Dose		Four-Week Loading Dose	
	No Pts	%	No Pts	%
Skin and mucous membranes	**10**	**100**	**10**	**100**
Rash	3	30	3	30
Pruritus	6	60	7	70
Sunburn	2	20	1	10
Dry Skin	5	50	5	50
Peeling	0	0	2	20
Finger tip peeling	2	20	2	20
Cheilitis	8	80	10	100
Skin fragility	0	0	2	20
Facial dermatitis	5	50	6	60
Alopecia	0	0	1	10
Dry hair	0	0	1	10
Dandruff	1	10	0	0
Gastro-intestinal	**4**	**40**	**9**	**90**
Soreness of mouth	2	20	2	20
Sore gums	0	0	1	10
Nausea	1	10	2	20
Anorexia	2	20	5	50
Thirst	1	10	4	40
Abdominal pain	2	20	2	20
Stomach ache	1	10	0	0
Spastic colon	0	0	1	10
Central nervous system	**6**	**60**	**3**	**30**
Headache	2	20	3	30
Insomnia	5	50	2	20
Special sensory	**6**	**60**	**5**	**50**
Eye pain	1	10	1	10
Irritation of eyes	6	60	5	50
Musculo-skeletal	**4**	**40**	**5**	**50**
Joint pain	1	10	5	50
Muscle cramp	3	30	2	20

Table 23 continued

Respiratory	**7**	**70**	**9**	**90**
Dry nose	7	70	7	70
Epistaxis	4	40	6	60
Sinus congestion	1	10	0	0
Miscellaneous	**4**	**40**	**5**	**50**
Lethargy	3	30	5	50
Fever	1	10	1	10
No. of adverse experiences	75		94	
Number of patients with adverse experiences	10	100	10	100
No. of patients treated	10		10	

TABLE 24

Clinical Adverse Experiences Group II - truncal acne

	Two-Week Loading Dose		Four-Week Loading Dose	
	No Pts	%	No Pts	%
Skin and mucous membranes	**10**	**100**	**10**	**100**
Rash	3	30	2	20
Pruritus	3	30	6	60
Sunburn	3	30	1	10
Dry Skin	9	90	10	100
Desquamation	2	20	3	30
Finger tip peeling	2	20	5	50
Cheilitis	10	100	10	100
Fragility of skin	0	0	1	10
Facial dermatitis	9	90	5	50
Hair loss	2	20	1	10
Paronychia	0	0	1	10
Gastro-intestinal	**5**	**50**	**5**	**50**
Nausea	1	10	0	0
Increased appetite	2	20	2	20
Anorexia	2	20	1	10
Thirst	3	30	2	20
Abdominal pain	1	10	1	10

Table 24 continued

Central nervous system	**3**	**30**	**6**	**60**
Headache	3	30	4	40
Insomnia	1	10	4	40
Special senses	**6**	**60**	**7**	**70**
Eyes - pain	2	20	2	20
Photophobia	1	10	4	40
Irritation of eyes	5	50	6	60
Musculo-skeletal	**1**	**10**	**2**	**20**
Joint pain	1	10	1	10
Muscle cramp	0	0	1	10
Respiratory	**9**	**90**	**9**	**90**
Dry nose	9	90	9	90
Epistaxis	5	50	7	70
Sinusitis	1	10	0	0
Miscellaneous	**1**	**10**	**3**	**30**
Lethargy	1	10	1	10
Fever	0	0	1	10
Number of adverse experiences reported	81		88	
Number of patients with adverse experiences	10	100	10	100
Number of patients treated	10		10	

There were no apparent differences between the adverse experiences reported in the two treatment schedules in either Group I or Group II.

In addition the adverse experiences reported by both Group I and Group II were similar in type and number.

Each of the 40 patients reported at least one adverse experience. The majority of adverse experiences were on the skin and/or mucous membranes. In no instance was dosage reduced or a patient removed from treatment because of the development of any clinical adverse experience.

Laboratory

Data obtained

The following routine blood and urine studies were obtained at baseline, weeks 1, 2 and 8:- FBC, WBC, differential, reticulocytes, platelets, haematocrit, complete urine analysis, fasting blood sugar, BUN and serum creatinine, serum albumin and total protein, serum bilirubin, SGOT, SGPT, alkaline phosphatase and LDH, cholesterol and triglycerides.

Assignation as a drug effect

Values outside the normal range of the laboratory were assigned in a "blind" manner as "remotely", "possibly" or "probably" related to the test medications according to guidelines in the protocol.

As the retinoids are new chemical entities and their effect on laboratory parameters could not be predicted, essentially all abnormalities were classified as at least possible unless they could be clearly categorised as remote. Thus many inconsequential laboratory abnormalities are included in the tables.

Tables 25 & 26 show the number and percentage of patients who had laboratory abnormalities classified as "probably" or "possibly" drug-related.

Tables 25 & 26/

TABLE 25

Number of laboratory abnormalities (low/high) in Group I

Facial Acne

Laboratory abnormalities	Two-Week Loading Dose						Four-Week Loading Dose					
	Low		High		Overall		Low		High		Overal	
	No	%	No	%	No	%	No	%	No	%	No	%
Haematologic												
Haematocrit %	1	10			1	10						
wbc	4	40			4	40	3	30	2	20	5	50
ESR			3	30	3	30			4	40	4	40
MCV	3	30			3	30	2	20			2	20
MCH	2	20			2	20						
MCHC			1	10	1	10			1	10	1	10
Reticulocytes	2	20			2	20	1	10			1	10
Lymphocytes							1	10			1	10
Atypical lympocytes									2	20	2	20
Platelets									2	20	2	20
PTT									2	20	2	20
Urinary												
wbc in urine			2	22	2	22						
rbc in urine			1	11	1	11						
bacteria in urine			1	11	1	11			3	30	3	30
Hepatic												
Alkaline phosphatase									1	10	1	10
Bilirubin									1	10	1	10
LDH									2	20	2	20
HDL	1	14			1	14						
Renal												
BUN	3	30			3	30	1	10			1	10
Serologic												
Immunoglobin M			1	10	1	10						
Miscellaneous chemistries												
Phosphorus			1	10	1	10						
Uric acid									1	10	1	10
Triglycerides									2	20	2	20
Number of adverse experiences reported	16		10		26		9		23		32	

TABLE 26

Number of laboratory abnormalities (low/high) in Group II

Truncal acne

Laboratory Abnormalities	Two-Week Loading Dose						Four-Week Loading Dose					
	Low		High		Overall		Low		High		Overall	
	No	%	No	%	No	%	No	%	No	%	No	%
Haematologic												
Haemoglobin	1	10			1	10	2	20			2	20
Haematocrit	1	10			1	10	1	10			1	10
rbc	1	10			1	10			1	10	1	10
wbc	3	30	1	10	4	40	3	30			3	30
Neutrophils			1	10	1	10						
Lymphocytes			1	10	1	10	1	10			1	10
Eosinophils			1	10	1	10						
Basophils			1	10	1	10						
Platelets			2	20	2	20			1	10	1	10
ESR			3	30	3	30			3	30	3	30
MCV	1	10			1	10	1	10			1	10
MCH	2	20			2	20	1	10			1	10
MCHC			1	10	1	10						
Reticulocytes	4	40			4	40	1	10	2	20	3	30
Prothrombin time			2	20	2	20	1	10			1	10
Monocytes									3	30	3	30
Urinary												
wbc in urine			1	10	1	10			3	30	3	30
rbc in urine			1	10	1	10			1	10	1	10
Bacteria in urine			3	30	3	30			4	40	4	40
Ca. oxalate crystals			1	50	1	50						
Serologic												
Immunoglobin G			2	20	2	20			2	20	2	20
Immunoglobin A			2	20	2	20						
Hepatic												
LDH			2	20	2	20						
Protein total			2	20	2	20			1	10	1	10
HDL	1	10			1	10	2	22			2	22
SGPT									3	30	3	30
Miscellaneous												
CO_2 content venous			1	10	1	10	1	10			1	10
Phosphorus			1	10	1	10						
Triglycerides			1	10	1	10			4	40	4	40
Uric acid									2	20	2	20
Number of adverse experiences reported	14		30		44		14		30		44	

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Group I

a) Two-week loading dose

There were 26 laboratory abnormalities possibly or probably related to ROACCUTANE, with 8 of the 10 patients having at least one abnormality. Those abnormalities thought to be possibly of clinical importance are discussed here.

Patient [redacted]: low MCV (normal range 79 - 82 cu microns). No baseline value but low levels at 12 and 16 weeks and at three follow-ups 5, 7 and 11 weeks post-therapy.

Patient [redacted]: low reticulocyte count (normal range 0.5 - Patient [redacted]: 1.5%). In patient [redacted] count was normal (1.1%) at baseline, but fell to 0.1% at two weeks and remained so throughout trial and at follow-up evaluation 0.3%. Patient [redacted], no baseline, low at 16 weeks (0.3%) and 19 days post-therapy (0.1%).

Patient [redacted]: rbc/hpf. This patient also has 5 rbc/hpf at 16 weeks and follow-up.

Patient [redacted]: high phosphorus (4.2 - 4.6mg/dl). From a normal baseline the level was elevated from week two until the 16-week evaluation, when it returned to normal.

Patient [redacted] low HDL (normal range 45 - 999mg/dl). From a baseline of 44mg/dl the level fell at two weeks to 30mg/dl and remained slightly low for the remainder of the trial and at follow-up (4 weeks post-therapy).

b) Four-week loading dose

There were 32 laboratory abnormalities possibly or probably related to ROACCUTANE with each of 10 patients treated having at least one abnormality.

Patient [redacted]: Atypical lymphocytes. Patient [redacted] had 1
Patient [redacted]: reported at 4 weeks, 9 at 8 weeks, none before or after. Patient [redacted] had 5 reported at 12 weeks, 4 at 16 weeks and 4 at follow up. (5 weeks post therapy).

Patient [redacted]: Elevated ESR. The baseline ESR was elevated (39mm/hr) and rose further to 76mm/hr at two weeks, but returned to 11mm/hr by the end of therapy.

Patient [redacted]: low MCV (83 - 98 cmm). No baseline evaluation and level at lower normal limit for first eight weeks, then slightly below normal at 12 weeks and 16 weeks returning to normal at follow-up (9 weeks post-therapy).

Patient [redacted]: low reticulocyte count, normal range (0.5 - 1.5%). Normal baseline, fell to 0.3% at two weeks, normal 1.4% at four weeks, fell at sixteen weeks 0.4%. There were two normal follow up evaulations.

Patient [redacted]: elevated PTT (normal range 25.8 - 38.6).

Patient [redacted]: Patient [redacted], normal at baseline 32.6 secs, elevated at 1 week 38.9, at 16 weeks 39.3 with normal values at all other times. Patient [redacted] elevated 40 secs after one day of therapy, but normal throughout remainder of treatment.

Patient [redacted]: elevated triglyceride level (normal range 50 - 200mg/dl). Normal baseline, increased to 302 at 4 weeks, thereafter fell to reach normal range at 16 weeks evaluation.

Group II

a) Two-week loading dose

There were 44 laboratory abnormalities, possibly or probably related to ROACCUTANE, with each of the 10 patients having at least one abnormality.

Patient [redacted]: eosiniphilia (normal range 1 - 5%). Normal counts except for 8% at each of the two follow up evaluations (4 and 8 weeks post therapy).

Patient [redacted]: basophilia (normal range 0 - 2%). 3% at 12 weeks and 3% at 16 weeks. At all other times within normal range.

Patient [redacted]: low reticulocyte count (normal range 0.5 -
Patient [redacted]: 1.5%).
Patient [redacted]: Patient [redacted], low at 4 weeks 0.2%, 8 weeks
Patient [redacted]: 0.3% and 4 weeks post therapy. In between it was normal at 12 and 16 weeks.

Patient [redacted] elevated baseline 1.8% and fell at 12 weeks 0.4% remaining low at 16 weeks and two follow ups. At the third follow up (12 weeks post therapy) it had returned to normal.

Patient [redacted] normal at baseline, fell at 12 and 16 weeks 0.3% returning to normal at follow up.

Patient [redacted] normal at baseline and throughout trial until 16 weeks when it fell 0.2% and remained low at follow up 6 weeks post therapy.

Patient [redacted]: elevated prothrombin time (normal range 10.5
Patient [redacted]: - 13.2 secs). Patient [redacted] one raised level 14.3 at 4 weeks, normal before and after. Patient [redacted] 17.9 secs at 16 weeks, normal before and after.

Patient [redacted]: rbc/hpf. rbc found in urine (> 5/hpf) at 2, 8, and 12 weeks.

Patient [redacted]: Calcium oxalate crystals in urine. Found on two occasions, 8 and 12 weeks.

Patient [redacted]: elevated immunoglobin G (normal range 72 -
Patient [redacted]: 204mg/dl). Patient [redacted] no baseline data, elevated 304 at 1 week only, normal thereafter. Patient [redacted] upper limit normal (204) at baseline, instantly elevated (254 - 274) during trial and follow up.

Patient [redacted]: elevated LDH (normal range 133 - 248 u).
Patient [redacted]: Patient [redacted] normal baseline, increased to 305 at two weeks normal thereafter. Patient [redacted] one elevated level 315u at 16 weeks, normal at all other times.

Patient [redacted]: decreased HDL (normal range 45 - 999mg/dl). Normal at baseline, fell at 4, 8 and 16 weeks (24 - 34). No follow up data.

b) Four-week loading dose

There were 44 laboratory abnormalities judged, possibly or probably related to ROACCUTANE with each of 10 patients treated having at least one abnormality.

Patient [redacted]: elevated monocyte count (normal range 4 - Patient [redacted] 8%). Patient [redacted] one elevation at 16 weeks. Patient [redacted]: Normal at all other times. Patient [redacted] elevated at 2 weeks (13%) and 8 weeks (11%), normal at all other times. Patient [redacted] one elevation only at 16 weeks (11%).

Patient [redacted]: low lymphocyte count (normal range 28 - 42%). Low baseline 14%, remained low until 12 weeks 30%.

Patient [redacted]: rbc in urine. 5 rbc/hpf seen at 1 and 2 weeks.

Patient [redacted]: SGPT elevated (normal range 2 - 45 units). All values normal at baseline, at 4 weeks SGPT was 108u.

Patient [redacted]: HDL low (normal range 45 - 999mg/dl). HDL fell to range 25 - 30mg/dl.

Patient [redacted]: Triglyceride (normal range 50 - 200). Triglycerides upper limit of normal 200mg/dl. All returned to normal at follow up.

Patient [redacted]: Triglycerides (normal range 50 - 200), HDL (normal range 45 - 999mg/dl). All values normal at baseline. From a base of 94mg/dl the triglycerides rose to 297 at 1 week and peaked at 836 at 16 weeks. HDL fell to 33mg/dl at 8 weeks and 21 at 12 weeks. The triglycerides returned to normal during follow-up 180mg/dl at 2 weeks post-therapy and 108mg/dl at 4 weeks post-therapy. The two follow up values of HDL were still low (30 and 32mg/dl).

2.3.9 Conclusion and Comment

This study shows that an initial loading dose of ROACCUTANE followed by a reduced maintenance dose is sufficient to produce a beneficial therapeutic response in cystic acne. The improvement is the same whether a two-week or a four-week loading dose is given.

2.3 SUMMARY OF INDIVIDUAL CLINICAL TRIAL IN ACNE

Head of Study: [redacted]

Investigators	Number of Pts	Centre
[redacted]	11	[redacted]
	4	
	5	
	6	
	10	
	15	
	5	
	8	
	13	
	14	
	11	
	10	
	8	
	11	
	14	
	17	
	9	
	12	
	17	
Total number of patients	200	

2.3.1 Type of Trial

An open multi-centre study of ROACCUTANE in acne conglobate and acne tetrad* with three dosage regimens.

The dosage regimens were: 0.2mg/kg/day
0.5mg/kg/day
and 1.0mg/kg/day

2.3.2 Demography, Criteria for Inclusion and Exclusion, Duration of Disease, Prior Treatment

200 patients entered the trial.

There were 189 evaluable patients - see 2.3.3.

Demography

The number of patients, their sex, age, height and weight are shown in Table 1.

Table 1/

* definition: Abstract Second Dermatopathology Symposium, London, UK, 12 - 15 July 1981.
Consists of: acne conglobata
hidradenitis suppuritiva
dissecting cellutitis of scalp
pilonidal sinus

TABLE 1

Demography of Patients in Trial

Number of patients	189
Male	172
Female	17
Mean age (yrs)	21.6
±SD	5.9
Range (yrs)	12-43
Height (cm)	178.2
±SD	8.3
Range (cm)	155-196
Weight (kg)	70.1
±SD	11.0
Range (kg)	40-110

There were 187 patients with acne conglobate, three patients also had acne tetrad and one patient had only acne tetrad.

Inclusion Criteria

1. Severe acne conglobate recalcitrant to other forms of therapy.
2. Either sex over 16 years. Women of childbearing potential must use an adequate contraceptive before, during and for three months after therapy with ROACCUTANE.
3. Good general health.

Exclusion Criteria

1. Pregnancy.
2. Impaired renal function.
3. Impaired hepatic function.
4. Hypertriglyceridaemia or other disorder of lipid metabolism.
5. Known sensitivity to retinoic acid or its analogues.
6. Radiation treatment for conglobate acne within the preceding six months.
7. Topical use of antibiotic ointments, retinoic acid, benzoyl peroxide, keratolytic agents, astringents, cryotherapy should be stopped at least 14 days before the start of therapy.
8. Systemic use of antibiotics, steroids and retinoids should be stopped at least 14 days before the start of therapy.
9. Unstable diabetes mellitus.

Duration of Disease

The mean duration of disease ±SD and range is shown in Table 2.

TABLE 2

Duration of Disease

Mean (yrs)	6.5
±SD	5.1
Range (yrs)	0.25 - 30.0

Prior Treatment

Data on all prior treatment was not available. Not all questionnaires were completed. From the data available 50% responded that nothing was successful. In 20% antibiotics were the most successful of prior treatments. In 81% of patients the activity of the disease was either static or deteriorating. All had acne conglobate recalcitrant to other forms of therapy.

2.3.3 Number of Patients Receiving ROACCUTANE, Number and Reasons for Interruption of Therapy, Deviations from Protocol

200 Patients received ROACCUTANE.

11 Patients interrupted therapy:

2 Patients [redacted] and [redacted] left the study for reasons unconnected to the study.

[redacted] was an [redacted]; [redacted]

[redacted].

The remaining nine patients interrupted therapy for the following reasons:

Patient [redacted] (0.5mg/kg/day) developed acute axillary-hidradenitis which was treated in another centre.

Patient [redacted] (0.5mg/kg/day) failed to report between weeks 4-14. Sufficiently reliable evaluation of clinical progress was not possible.

Patient [redacted] (1.0mg/kg/day) experienced cheilitis, facial dermatitis and general weakness, and failed to report for examination at 12 weeks.

Patient [redacted] (1.0mg/kg/day)	elevation of SGOT and SGPT after three weeks therapy. Clinical response recorded as satisfactory. Values returned to normal three weeks after cessation of therapy.
Patient [redacted] (1.0mg/kg/day)	Treatment stopped after two weeks because of disturbance of conciousness of unclear nature, disordered vision, impaired concentration and high rate of hair loss.
Patient [redacted] (1.0mg/kg/day)	This patient's treatment was intermittent and of varying dosage. [redacted] was excluded on grounds of deviation from protocol.
Patient [redacted] (0.2mg/kg/day)	Treatment ceased after two weeks because of severe pains in the thighs resembling pains after strenuous exercise.
Patient [redacted] (1.0mg/kg/day)	Treatment was stopped because of a cure before the end of the trial.
Patient [redacted] (1.0mg/kg/day)	Treatment stopped after two weeks because of deterioration of acne.

2.3.4 Daily Dosage

Table 3 shows the mean daily dose; SEM, range and number of patients in each dose regime.

TABLE 3

Mean daily dose (mg/kg); SEM; Range and Number of Patients

Dose Regime	Number of Patients	Mean	SEM	Range
Low	51	0.209	0.004	0.142-0.277
Middle	69	0.495	0.006	0.192-0.682
High	80	1.001	0.004	0.794-1.091

2.3.5 Duration of Therapy

The duration of therapy was 12 weeks.

2.3.6 Nature of Treatment of Control Group

There was no control group.

2.3.7 Results - Efficacy

The patients were assessed at two week intervals for 12 weeks.

1. Parameters measured

   a) All lesions were counted namely:

      i) open comedones

      ii) closed comedones

      iii) papules

      iv) pustules

      v) nodules

   b) Seborrhoea of forehead and scalp were assessed and recorded according to the following four point scale:

      none = 0

      slight = 1

      moderate = 2

      severe = 3

2. Analysis

   Being an open, multicentre, non-randomised trial, selection bias was unavoidable. In fact the 1.0mg/kg/day group had the most severe acne - see Table 4.

Comparisons of the three dose regimens on clinical efficacy is difficult.

There was, however, no manifest differences between the patients of the three dose regimens with respect to case history criteria and demography. Therefore, dose/side-effect relationships could be analysed.

Group validation of efficacy without a comparative placebo group is difficult. However, 81% of patients had severe acne either worsening or showing no change over duration of 6.5 years. With this background a good response would be clinically significant.

3. Results - lesion counts

Table 4 shows the mean ±SD lesion counts at each assessment for all three dose regimens.

Table 4/

TABLE 4

Mean ±SD lesion counts each week for each dose regime

Lesion	Dose mg/kg/day	0 Weeks	2 Weeks	4 Weeks	6 Weeks	8 Weeks	12 Weeks	% mean improvement
Open Comedone ± SD	0.2	93 ± 145	77 ± 117	58 ± 79	40 ± 55	46 ± 61	36 ± 47	61
	0.5	93 ± 101	83 ± 92	72 ± 92	61 ± 78	61 ± 82	51 ± 72	45
	1.0	182 ± 215	153 ± 205	114 ± 164	87 ± 117	67 ± 99	52 ± 75	71
Closed Comedone ± SD	0.2	49 ± 53	49 ± 62	42 ± 60	49 ± 61	36 ± 51	42 ± 52	14
	0.5	109 ± 125	103 ± 131	96 ± 127	91 ± 131	78 ± 122	65 ± 113	40
	1.0	109 ± 144	95 ± 129	79 ± 107	64 ± 94	51 ± 88	45 ± 86	59
Papules ± SD	0.2	78 ± 73	66 ± 64	59 ± 61	59 ± 56	41 ± 44	43 ± 53	45
	0.5	65 ± 73	56 ± 44	45 ± 32	34 ± 29	32 ± 27	32 ± 28	51
	1.0	119 ± 166	104 ± 145	72 ± 95	50 ± 61	34 ± 39	27 ± 28	77
Pustules ± SD	0.2	17 ± 25	12 ± 14	8 ± 9	6 ± 6	7 ± 11	3 ± 4	82
	0.5	34 ± 38	24 ± 27	17 ± 28	15 ± 33	14 ± 25	10 ± 23	71
	1.0	29 ± 33	18 ± 27	9 ± 10	8 ± 9	5 ± 7	4 ± 6	86
Nodules ± SD	0.2	10 ± 6	7 ± 5	6 ± 5	6 ± 5	4 ± 3	5 ± 6	50
	0.5	13 ± 10	12 ± 9	10 ± 8	8 ± 7	6 ± 5	4 ± 5	69
	1.0	13 ± 11	9 ± 8	6 ± 6	5 ± 6	4 ± 4	4 ± 5	69

Table 4 continued

Number of patients evaluated

Week	0	2	4	6	8	12
Open comedones	189	189	189	173	184	168
Closed comedones	189	188	189	173	182	167
Papules	189	188	189	174	184	167
Pustules	189	186	188	173	182	166
Nodules	189	189	189	172	180	164

Table 5 shows the number of patients whose lesion count improved by 75% or more, after 12 weeks treatment, for each type of lesion and for each dose regimen.

TABLE 5

Number of patients whose lesions improved by > 75%

	Dose mg/kg/day	Total No Pts	No of Pts 'improved'	%
Open Comedones	0.2	37	12	32
	0.5	62	26	42
	1.0	69	43	62
Closed Comedones	0.2	38	8	21
	0.5	68	29	43
	1.0	66	35	53
Pustules	0.2	32	28	88
	0.5	65	52	80
	1.0	64	62	96
Nodules	0.2	39	26	67
	0.5	59	34	58
	1.0	56	44	79

All lesions improved. However, there was a wide variance of results at each assessment. A greater percentage of patients achieved a 75% improvement in each type of lesion on the highest dose. The severer inflammatory lesions, pustules and nodules, responded to treatment to a greater extent than the non-inflammatory comedones. Statistical analysis is not possible.

Results: evaluation of seborrhoea

Table 6 shows the number of patients with each grade of seborrhoea of the forehead at baseline and at 12 weeks.

TABLE 6

Evolution of seborrhoea of the forehead:

Number of patients in each grade

Dose		Baseline no of pts	%	After 12 weeks no of pts	%
0.2mg/kg	none	2		29)	
	slight	3		13)	84%
	moderate	21)		7	
	severe	24)	90%	1	
		--		--	
	Total	50		50	
		--		--	
0.5mg/kg	none	6		42)	
	slight	6		18)	91%
	moderate	31)		5	
	severe	23)	82%	0	
		--		--	
	Total	66		66	
		--		--	
1.0mg/kg	none	3		64)	100%
	slight	9		9)	
	moderate	41)		0	
	severe	20)	84%	0	
		--		--	
	Total	73		73	
		--		--	

Table 7 shows the number of patients with each grade of seborrhoea of the scalp at baseline and after 12 weeks.

TABLE 7

Evolution of seborrhoea of the scalp

Dose		Baseline no of pts	%	After 12 weeks no of pts	%
0.2mg/kg	none	0		26)	
	slight	2		15)	82%
	moderate	19)		7	
	severe	29)	96%	2	
		--		--	
	Total	50		50	
		--		--	
0.5mg/kg	none	4		43)	
	slight	10		21)	97%
	moderate	34)		1	
	severe	18)	79%	0	
		--		--	
	Total	66		66	
		--		--	
1.0mg/kg	none	4		60)	
	slight	8		11)	97%
	moderate	28)		2	
	severe	33)	84%	0	
		--		--	
	Total	73		73	
		--		--	

In all dose regimens there was a marked decrease in seborrhoea of the facial skin and scalp.

2.3.8 Adverse Reactions

Clinical

The following 12 side-effects were recorded and their incidence, maximum intensity at each dose is shown in Table 8.

Table 8/

TABLE 8

Incidence and maximum observed intensity of 12 side-effects

Side Effect	Dose mg/kg	Incidence	Maximum intensity Slight	Moderate	Severe
Dryness of the lips	0.2	97.96%	6.12%	24.49%	67.35%
	0.5	100.00%	4.23%	25.35%	70.42%
	1.0	100.00%	6.33%	40.51%	53.16%
Dryness of the mouth	0.2	28.00%	24.00%	2.00%	2.00%
	0.5	39.44%	23.94%	15.49%	0.00%
	1.0	50.63%	31.65%	15.19%	3.80%
Dryness of the nose	0.2	62.00%	28.00%	28.00%	6.00%
	0.5	61.97%	30.99%	12.68%	18.31%
	1.0	83.54%	29.11%	37.97%	16.46%
Cheilitis	0.2	66.00%	24.00%	30.00%	12.00%
	0.5	81.69%	16.90%	29.58%	35.21%
	1.0	97.47%	24.05%	49.37%	24.05%
Desquamation of the skin	0.2	60.00%	46.00%	14.00%	0.00%
	0.5	84.51%	47.89%	29.58%	35.215
	1.0	84.81%	37.97%	40.51%	6.33%
Thinning of the skin	0.2	9.80%	9.80%	0.00%	0.00%
	0.5	14.08%	14.08%	0.00%	0.00%
	1.0	26.58%	22.78%	3.80%	0.00%
Vulnerability of the skin	0.2	23.53%	21.57%	1.96%	0.00%
	0.5	32.39%	15.49%	15.49%	1.41%
	1.0	53.16%	44.30%	5.06%	3.80%
Alopecia	0.2	9.80%	9.80%	0.00%	0.00%
	0.5	28.17%	25.35%	1.41%	1.41%
	1.0	27.85%	24.05%	2.53%	1.27%
Facial dermatitis	0.2	21.57%	13.73%	7.84%	0.00%
	0.5	56.34%	46.48%	5.63%	4.23%
	1.0	91.14%	58.23%	29.11%	3.80%
Pruritus	0.2	39.22%	33.33%	5.88%	0.00%
	0.5	53.52%	33.80%	15.49%	4.23%
	1.0	54.43%	48.10%	5.06%	1.27%
Conjunctivitis	0.2	13.73%	9.80%	1.96%	1.96%
	0.5	25.35%	16.90%	7.04%	1.41%
	1.0	45.57%	39.24%	3.80%	2.53%
Muscular pains	0.2	7.84%	1.96%	1.96%	3.92%
	0.5	14.08%	9.86%	2.82%	1.41%
	1.0	16.46%	11.39%	3.80%	1.27%

The above data shows four types of dose-side effect relationships.

Type I Plateau reached 0.2mg/kg.
All patients suffer from side-effects.
Only applies to dry lips.

Type II A 'linear' dose-side effect relationship.
This applies to dryness of mouth, cheilitis, thinning of skin, vulnerability of skin, facial dermatitis and conjunctivitis.

Type III Plateau at 0.2 and 0.5mg/kg/day.
1.0mg/kg/day showing markedly higher incidence of side-effects.
This applies only to dryness of nasal mucosa.

Type IV Plateau at 0.5 and 1.0mg/kg/day.
The incidence in the 0.2mg/kg/day being much lower. This applies to desquamation of skin, alopecia, pruritus and muscular pains.

Other side-effects reported are shown in Table 9.

Table 9/

TABLE 9

Additional side-effects under ROACCUTANE

(3 dosage groups)

Patient Number	Dose mg/kg/day	General symptoms
[redacted]	0.5	Impairment of general condition
	1.0	Tiredness
	1.0	General weakness
	1.0	Tiredness, poor concentration

Patient Number	Dose mg/kg/day	Other undesirable effects
[redacted]	0.2	Abdominal pains, irritation cough
	0.5	Epididymitis
	0.5	Joint pains
	0.5	Pain in the chest
	0.5	Loss of libido
	1.0	Muscular weakness
	1.0	Muscular weakness in the arms
	1.0	Blepharitis
	1.0	Pain in the back
	1.0	Feeling of pressure in the eyes

Patient Number	Dose mg/kg/day	Various dermatological effects
[redacted]	0.2	Ulceration of the elbows
	0.2	Epistaxis
	0.5	Epistaxis
	0.5	Pruritus of the arms

Patient Number	Dose mg/kg/day	Various dermatological effects
[redacted]	0.5	Epistaxis
	0.5	Epistaxis
	0.5	Hirsutism
	0.5	Epistaxis
	0.5	Epistaxis
	0.5	Epistaxis
	0.5	Seborrhoea, eczema on the upper arms and back
	0.5	Epistaxis and pruritus over the eyes
	1.0	Paronychia
	1.0	Desquamation of the scalp
	1.0	Desquamation of the scalp
	1.0	Dryness of the nasal mucosa, epistaxis
	1.0	Greasy feeling of the hands
	1.0	Paronychia
	1.0	Palmar hyperhidrosis
	1.0	Rhagades
	1.0	Epistaxis
	1.0	Epistaxis
	1.0	Epistaxis

Laboratory

The laboratory values, mean ±SD and ranges are given in Table 10.

Table 10/

TABLE 10

Mean ±SD Laboratory Values at 0, 2, 4, 12 weeks for three dosages, 0.2, 0.5, 1.0mg/kg/day

Laboratory Parameter Mean ±SD	WEEK 0			2			4			12		
	0.2	0.5	1.0	0.2	0.5	1.0	0.2	0.5	1.0	0.2	0.5	1.0
Haemoglobin ± g/dl	14.9 1.2	15.0 1.6	15.1 1.2	14.6 1.3	14.8 1.4	15.2 1.2	14.7 1.3	15.1 2.2	15.1 1.2	14.9 1.2	14.5 1.7	15.2 1.3
Erythrocytes x $10^6 cm^{-1}$	5.0 0.5	5.1 0.4	5.0 0.4	4.9 0.6	5.0 0.4	5.1 0.5	4.9 0.5	5.0 0.5	5.0 0.5	4.9 0.5	4.9 0.5	5.0 0.5
Leucocytes x 10^3 cm^{-1}	7.9 2.2	7.6 2.2	8.7 2.5	7.7 2.5	7.7 2.2	8.1 2.2	7.5 1.9	7.2 2.2	7.7 2.5	6.9 1.7	7.1 2.5	7.5 2.5
Neutrophils %	61 10	62 12	61 10	59 13	63 11	61 11	62 13	61 10	59 13	53 12	57 12	56 10
Eosinophils %	3 2	3 2	2 2	3 4	2 2	2 2	3 2	2 2	2 2	2 2	2 2	2 2
Basophils %	0.7 0.9	0.6 0.8	0.4 0.7	0.6 0.7	0.4 0.8	0.5 0.7	0.5 0.9	0.7 1.0	0.4 0.8	0.6 0.8	0.7 1.0	0.5 0.8
Monocytes %	4.0 2.6	4.4 3.5	5.9 3.5	5.0 3.5	4.5 3.1	5.2 3.1	3.8 3.0	5.4 5.0	4.8 3.2	4.8 3.4	4.7 3.7	5.9 3.0
Lymphocytes %	31 10	31 11	30 10	32 12	30 10	31 11	32 11	32 10	33 12	39 10	37 12	35 9
Platelets x 10^3	218 62	239 47	272 85	224 57	248 60	275 73	217 49	240 49	274 74	209 50	239 65	262 67
Bilirubin mg/dl	0.5 0.2	0.6 0.3	0.7 0.4	0.6 0.2	0.5 0.2	0.6 0.1	0.6 0.3	0.4 0.2	0.5 0.2	0.5 0.2	0.4 0.2	0.5 0.2
Alk.phosphatase u./l	156	167 65	135 76	143 50	166 65	135 73	148 54	164 63	130 64	147 60	169 83	130 66
SGPT u/l	12 10	11 6	13 7	12 9	12 5	13 4	12 10	11 5	14 10	11 9	11 5	13 7
SGOT u/l	11 8	10 4	12 5	11 4	10 3	12 3	11 5	11 4	13 7	11 6	10 3	13 5
Creatinine mg/dl	1.0 1.0	0.9 0.1	0.9 0.2	1.0 0.1	0.9 0.2	0.9 0.2	1.1 0.2	0.9 0.1	0.9 0.2	1.0 0.2	0.9 0.2	0.9 0.2
Cholesterol mg/dl	167 38	174 39	172 39	176 41	164 31	188 40	173 39	171 31	200 44	178 36	175 31	204 44
Triglycerides mg/dl	131 111	90 51	100 54	142 131	121 82	131 76	132 75	130 80	140 81	139 92	139 98	147 90

Table 11 shows the number of patients with laboratory findings above or below the limits of the normal range as defined at each test centre.

TABLE 11

Variation of some laboratory parameters with time

This table shows the numbers of patients with laboratory findings above or below the limited of the normal range as defined at each test centre.

Laboratory Parameter	Dose mg/kg	0	2	4	12 weeks
Haemoglobin reduced	0.2	8	9	10	7
	0.5	13	14	12	16
	1.0	7	5	7	5
Leucocyte count raised	0.2	11	12	12	4
	0.5	10	6	6	10
	1.0	24	16	15	8
Platelet count reduced	0.2	0	1	0	1
	0.5	0	0	0	1
	1.0	4	2	4	4
Bilirubin raised	0.2	2	2	2	1
	0.5	2	0	0	1
	1.0	6	0	1	0
Alkaline phosphatase raised	0.2	15	12	12	10
	0.5	19	18	20	22
	1.0	25	24	21	22
SGPT raised	0.2	3	3	3	4
	0.5	4	4	4	0
	1.0	7	5	6	6
SGOT raised	0.2	2	2	1	3
	0.5	1	0	2	0
	1.0	6	1	6	6
Creatinine raised	0.2	3	2	5	3
	0.5	1	2	2	4
	1.0	2	1	0	0

Table 12 shows the numbrs of patients with increased values for serum cholesterol and serum triglyceride during the trial having had a value that was normal at baseline. Values that were abnormal at baseline are shown.

TABLE 12

Numbers of patients with abnormal serum cholesterol and triglyceride values

	Dose mg/kg	Increased value	Abnormal at baseline	Normal
Cholesterol	0.2	0	2	43
	0.5	0	1	65
	1.0	13*	1	52
Triglycerides	0.2	4	5	30
	0.5	7	3	56
	1.0	15**	1	51

* $p = 0.0001$ χ^2 test

** $p = 0.0349$ χ^2 test

2.3.9 Conclusion and Comment

In the three dosages 0.2, 0.5 and 1.0mg/kg/day of ROACCUTANE the percentage of open comedones improved, by 75% or more, were 24%, 29% and 56% and the percentage of closed comedones improved were 21%, 43% and 53%, respectively.

The percentage of pustules and nodules improving to the same extent on the three dose regimens were 88%, 80% and 96% and 67%, 58% and 79% respectively.

The criteria of improvement by 75% or more is stringent bearing in mind that improvements in the symptoms of acne by 30 - 50% are often rated treatment successes. 81% of these patients had acne that was either static or actually deteriorating and had a mean duration of disease of 6.5 years of severe conglobate acne largely refractory to conventional therapy. There can be no reasonable doubt that treatment with ROACCUTANE was effective.

Despite the occurrence of expected side-effects on skin and mucous membranes affecting all patients, 95.5% of 200 patients completed the 12 week course of therapy. Only four (21%) of the withdrawals were due to drug related effects. One patient withdrew because of cure of [redacted] acne conglobate.

There was a tendency to increased serum lipids and alkaline phosphatase during the course of the disease and these levels should be monitored at one or two monthly intervals.

The investigator states that as a rule ROACCUTANE should be started at 0.5mg/kg/day and continued at this dose until marked improvement or cure is achieved which usually takes 12 weeks.

In unusually severe conglobate acne, fulminant acne or acne tetrad, treatment should be started with 1.0mg/kg/day and maintained for 12 weeks. The dose may be reduced to 0.5mg/kg/day if marked improvement is observed.

In the less severe conglobate acne and papulo-pustular acne treatment may begin with 0.2mg/kg/day with the option of increasing dosage within 8 - 12 weeks if the response is unsatisfactory.

Dosage reduction may be necessary in the event of severe clinical side effects or abnormal laboratory values. Particular care should be taken with those patients with risk factors tending to elevation of liver enzymes and serum lipids such as diabetes mellitus, obesity, familial hypercholesterolaemia and triglyceridaemia and alcoholism.

Pregnancy is an absolute contraindication and women of childbearing potential should use an adequate contraception before during and for three months after cessation of therapy.

3. ADVERSE REACTIONS

3. Adverse Reactions

ROACCUTANE causes clinical adverse reactions in virtually all patients. The skin and mucous membranes are affected mostly. The table below is the percent incidence of clinical side effects from all 451 patients in the studies in the submission.

Cheilitis	96
Dry skin	22
Facial dermatitis	55
Desquamation	50
Pruritus	30
Dry nose	57
Epistaxis	10
Irritation of the eyes	11
Conjunctivitis	19
Joint pain	13
Alopecia	13
Pain in the eyes	1

These effects are predictable and reversible. The same side-effects occur with hypervitaminosis A and with the marketed retinoid, TIGASON. However the two retinoids, ROACCUTANE and TIGASON do not share the liver, bone and CNS toxicity that complete the rest of the hypervitaminosis A syndrome.

Several studies ([redacted]) in the submission have made detailed ophthalmological examinations. There have been no adverse reactions other than those common to the muco-cutaneous features mentioned above namely - conjunctivitis and belpharitis.

Occasionally a keratitis and a staphylococcal conjunctivitis have been reported. Blackman's extensive investigations support these findings.

The overall withdrawal incidence for adverse clinical reactions was 1.1%.

As a whole these clinical adverse reactions have been mild in severity and readily tolerated by the patients.

The two laboratory abnormalities that are of concern during use of ROACCUTANE are elevation of liver enzymes and serum lipids.

[redacted] in [redacted] found a dose related disturbance of SGOT and SGPT in a minority of patients. [redacted] found that the elevation from baseline at the end of the four month course of treatment was statistically significant for the two higher doses (0.5 and 1.0mg/kg/day; $p < 0.005$; 0.1mg/kg/day causing no elevation). However the mean value only ever rose above the normal range on one occasion.

[redacted] also noted a statistically significant elevation from baseline values at the end of treatment for serum triglycerides and serum cholesterol ($p < 0.005$). Again the mean values were within normal range.

In those few individuals with values outside the normal range, half were transient elevations and the remainder not particularly high. Those individuals with pre-existing abnormal values did not show any marked elevations during ROACCUTANE treatment.

Plewig has shown that hypertriglyceridaemia is dose related. 0.2mg/kg/day dosage was not associated with an elevations and 2.0mg/kg/day with clearly greater elevations than 1mg/kg/day[2].

The greatest elevations have occurred in the USA in non-acne patients with dose up to 4mg/kg/day[3,4]. Gollnick[5] has confirmed to dose-dependency of the elevations of serum triglycerides and cholesterol. He found that abnormal values occurred only in the association with well-established 'risk factors' including a family history of blood lipid disorders, alcoholism, obesity and smoking.

In the dose range recommended 0.1 - 1.0mg/kg/day the risk of elevation of triglycerides and/or cholesterol is small. Should it occur however, half the elevations are transient, the duration of treatment is limited (12 - 16 weeks), dietary manipulation without dosage adjustment may correct the elevation and in the last event they are readily reversible on reduction or cessation of dosage.

The overall incidence of withdrawals for abnormal laboratory values was 0.2%.

The appropriate warnings related to the possibility of elevation of liver enzymes and serum triglycerides are given in our data sheet.

1. Blackman H. J. et al 'Blepharoconjunctivitis a side-effect of oral 13-cis retinoic acid therapy for dermatologic disease' Ophthalmology, 1979; 86, 753-58.

2. Plewig G et al. Effects of two retinoids in animal experiments and after clinical application in acne patients: 13-cis retinoic acid Ro 04-3780 and aromatic retinoid Ro 10-9359 in 'Retinoids: Advances in Basic Research and Therapy' Orfanos C E et al. Springer-Verlag, Berlin, 1981, 219-35.

3. Nigra T P et al. 'Elevation of serum triglyceride levels from oral 13-cis retinoic acid' in 'Retinoids: Advances in Basic Research and Therapy' Orfanos C E et al. Springer-Verlag, Berlin, 1981, 219-35.

4. Gross E, et al. 'Elevated plasma lipids with oral retinoids'. J Invest Derm, 1981, 76, 303-4.

5. Gollnick H et al. 'Risk factors promote elevations of serum lipids in acne patients under oral 13-cis retinoic acid (isotretinoin)' Arch Derm Res, 1981, 271, 189-96.

4. SAFETY in relation to EFFICACY in clinical use of ROACCUTANE

The efficacy of ROACCUTANE in treating cystic and conglobate acne and severe acne resistant to systemic antimicrobial therapy is demonstrated in this submission.

The problem of toxicity of ROACCUTANE is resolved by showing:

a) the benefit of the drug in the chosen indication outweighs the risks, and
b) the use of the drug will be under the supervision of dermatologists.

The toxicity of ROACCUTANE has been dealt with extensively in this submission and full reference to adverse effects is made in the proposed data sheet.

Like all analogues of Vitamin A, ROACCUTANE has part of the toxicity of Retinol affecting the skin and mucous membranes. It does not have the toxic affects on the skeletal, central nervous or hepatic systems. However it is known that at doses above the recommended level, dose-related elevations of liver enzymes and serum triglycerides occur. Infrequently these elevations occur at recommended dosages. For this reason we have stated that these values should be monitored before and during treatment.

From our studies it appears that these elevations occur particularly if other 'risk factors' are present, eg obesity, diabetes mellitus, alcoholism, cigarette smoking and family history of hyperlipidaemia. It may be possible by dieting and change of life style to bring abnormal values of serum lipids to within the normal range without adjusting the dose of ROACCUTANE. However, like all the side effects, these elevations are reversible on reduction or cessation of therapy. In practice they are not a problem.

The theoretical risks of a temporarily raised serum triglyceride, or even more rarely serum cholesterol, associated with or without a decrease in high density hipoproteins is presently contentious and must be viewed in the light of the indication and the likely duration and frequency of treatment.

The dramatic results in cystic acne, conglobate acne and severe acne vulgaris resistant to systemic antimicrobials has been demonstrated. These patients will have, unless of the sturdiest nature, severe psychological stress, at a time in their lives when personal appearance is particularly important. The impact of a really effective treatment for the first time on these young lives is considerable.

Not only is the benefit psychological. If severe acne resistant to systemic antimicrobial therapy is successfully treated with ROACCUTANE, as has been demonstrated by Cunliffe et al, there is real hope that the disease in these patients will not progress to 'ice-pick' scarring that distorts their features thereafter.

We have present evidence that at 0.5mg/kg daily - or upto 1.0mg/kg/daily in unresponsive cases - produces clearing of acne in the majority of patients and a prolonged remission ensues. It is too soon to present data as to the length of the average remission but one or two treatments does seem to be sufficient for the majority. There is a clear impression that lower doses of ROACCUTANE 0.1 - 0.2mg/kg/day although initially effective in clearing acne gives shorter remissions. The lower doses are, therefore, less reliably effective and are only recommended for patients who show poor tolerence at 0.5mg/kg/day. We have presented data of remissions as long as 20 months. The possible risk of elevated serum triglycerides at sometime during a 3-4 month, once or twice only therapy, seems a very small risk to take for the sure benefits of therapy.