2.3 SUMMARY OF INDIVIDUAL CLINICAL TRIAL IN ACNE

Redacted under Section 40 of the FOIA.

2.3.1 Type of Trial

A double blind-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	8	8
Male	8	8
Female	0	0
Mean age (yrs)	20.5	20.8
Range	[redacted]	
Mean Duration of Disease (yrs)	5.4	6.0
Range	2.2 - 9.7	2.1 - 11.4

Redacted under Section 40 of the FOIA.

There was no difference in sex, age or duration of disease between the two groups.

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 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 exacerbated by the superimposition of symptoms of hypervitaminosis A.
5. Dietary variation resulting in excessive intake (greater than 50,000 i.u./day of Vitamin A).

Prior Treatment

Before entry into the trial all the patients 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 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, Deviation from Protocol

There were eight patients in both the ROACCUTANE and the TIGASON groups. Redacted under Section 40 of the FOIA.

Two patients [redacted] were lost to follow-up after completing the eight-week double blind phase.

2.3.4 Daily Dosage

The mean daily dose in both groups is shown in Table 2.

TABLE 2

Mean Daily Dosage mg/kg

	ROACCUTANE	TIGASON
Mean	0.99	0.99
±SEM	0.05	0.02
Range	0.91-1.08	0.95-1.04

2.3.5 Duration of Dosage

The duration of therapy of both ROACCUTANE and TIGASON was 57 days.

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 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

c) Sebum production

Collection 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 at the end of treatment.

Reference

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

TABLE 3

Mean total cyst count + SEM

	ROACCUTANE			TIGASON			
Week	Cysts	% Change	No.⊕ Pts	Cysts	% Change	No. Pts	p‡
Baseline	48.7		7	27.6		8	
±	21.7			9.5			
2 weeks	63.3	+30	7	32.0	+16	8	0.771
±	24.0			9.6			
4 weeks	40.1	-18	7	27.8	+0.5	8	0.344
±	9.9			3.7			
8 weeks	32.7	-33	7	32.9	+19	8	0.215
±	12.5			5.4			
4 weeks off drug	13.2	-76	6	36.7	+20	7	0.048
±	3.2			12.0			
8 weeks off drug	11.0	-80	6	27.3*	-0.4	8	0.071
±	2.4			5.5			

‡ Two-sample t-test comparison of treatment mean changes.

* p = 0.012 two-sample test comparison of treatment means.

There was a 33% decrease in total number of cysts after eight weeks in the ROACCUTANE group as opposed to a 19% increase in total number of cysts in the TIGASON group.

⊕ One patient had less than 10 lesions at baseline and was not included in this or any subsequent evaluation in which the number of lesions were counted. However, his data is included in the global evaluations and in the safety data.

The within-group changes from baseline and the comparative change from baseline between the two treatment groups at end of therapy did not reach statistical significance.

However at four weeks off drug there was a statistically significant difference between the drugs, with ROACCUTANE giving the better results ($p = 0.048$).

Cyst Count - Face

Table 4 shows the mean facial cyst count before, during and at the end of treatment.

TABLE 4

Mean Facial Cyst Count +SEM

	ROACCUTANE			TIGASON			
	Cysts	% Change	No. Pts	Cysts	% Change	No. Pts	p‡
Baseline	9.0		7	2.6		8	
±	3.0			1.3			
2 weeks	14.7	+64	7	5.0	+91	8	0.742
±	5.0			1.6			
4 weeks	7.1	-21	7	6.1	+133	8	0.055
±	1.9			1.4			
8 weeks	5.1	-42	7	7.3	+176	8	0.032
±	2.2			2.2			
4 weeks off drug	2.3*	-77	6	7.6	+253	7	0.002
±	0.9			1.7			
8 weeks off drug	2.2*	-78	6	6.0	+129	8	0.007
±	0.5			1.5			

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

‡ Two-sample t-test comparison of treatment changes.

After eight weeks of treatment and at four and eight weeks off drug there was a statistically significant difference between the two drugs in the mean change from baseline in the number of cystic lesions on the face, with ROACCUTANE giving the better results.

Cyst Count - Back and Chest

Similar results, although not statistically significant, occurred with the 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 +SEM at eight weeks

	ROACCUTANE			TIGASON			
Area	Change mean no. cysts	%	No. Pts	Change mean no. cysts	%	No. Pts	p‡
Total ±	-16.0 24.6	-33	7	+5.3 5.9	+19	8	0.215
Face ±	-3.9 3.6	-43	7	+4.6 1.7	+17	8	0.032
Chest ±	-4.1 8.0	-40	7	+0.4 1.3	+7	8	0.298
Back ±	-8.0 13.5	-27	7	+0.3 5.5	+1	8	0.294

‡ Two-sample t-test comparison of treatment changes

Table 6 shows the change in mean number of cysts eight weeks after discontinuation of therapy whilst the double-blind status was maintained.

TABLE 6

Changes in mean number of cysts +SE eight weeks post therapy

	ROACCUTANE			TIGASON			
Area	Change mean no. cysts	%	No. Pts	Change mean no. cysts	%	No. Pts	p‡
Total ±	-43.5 24.3	-80	6	-0.4 7.7	-1	8	0.071
Face ±	-7.8* 3.1	-78	6	+3.4 1.2	+129	8	0.007
Chest ±	-10.7 7.4	-91	6	-0.1 1.3	+2	8	0.103
Back ±	-25.0 14.1	-76	6	-3.9 6.8	-20	8	0.108

‡ Two-sample t-test comparison of treatment change.

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

Patients' and Physician's Global Evaluations

Table 7 shows the mean subjective scores at eight weeks and at four weeks off drug in both groups of patients, as assessed by the physician.

TABLE 7

Mean scores Physician's Global Evaluation

	ROACCUTANE			TIGASON			
Week	Score	±SE	No. Pts	Score	±SE	No. Pts	p*
Week 8	1.25	0.49	8	0.00	0.33	8	0.028
4 weeks off drug	0.86	0.60	7	-0.25	0.49	8	0.088

* 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

Table 8 shows the mean subjective scores as assessed by the patients.

TABLE 8

Mean scores Patients' Global Evaluation

	ROACCUTANE			TIGASON			
Week	Score	±SE	No. Pts	Score	±SE	No. Pts	p*
Week 8	1.38	0.50	8	0.25	0.41	8	0.052
4 weeks off drug	0.29	0.61	7	-0.38	0.46	8	0.201

* 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 9 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 9

Number of patients achieving different levels of improvement

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

* compared to end of therapy

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 10.

Table 10/

TABLE 10

Mean Sebum Production (mg/10cm^2/3hr)

	ROACCUTANE			TIGASON			
Week	Sebum	% Change	No. Pts	Sebum	% Change	No. Pts	p‡
Baseline	4.27 ± 1.45		8	3.65 ± 1.08		8	=0.825
2 weeks	1.53* ± 0.71	-64	8	3.62 ± 0.87	-1	8	<0.001
4 weeks	0.82* ± 0.64	-80	7	3.42 ± 0.99	-6	8	<0.001
8 weeks	0.63* ± 0.51	-85	8	3.15* ± 0.70	-14	8	<0.001
4 weeks off drug	2.47* ± 1.32	-40	7	3.28 ± 0.72	-10	8	=0.045
8 weeks off drug	3.39 ± 1.78	-14	6	2.91* ± 1.02	-20	8	=0.675

* $p < 0.05$ change from baseline

‡ Level of statistical significance of the difference between the groups.

At all points during therapy and for four weeks after treatment was stopped the decrease from baseline was statistically significant for patients receiving ROACCUTANE.

At eight weeks on therapy and at eight weeks off drug the decrease was also statistically significant for TIGASON.

The difference between the two therapies was statistically significant at 2, 4 and 8 weeks of therapy and at 4 weeks post therapy, with ROACCUTANE giving the greater decrease in sebum production.

Figures 1 and 2 show the % change in cyst count and sebum production in both treatment groups.

Figures 1 and 2

FIGURE 1

% Change in Cyst Count in Both Treatment Groups

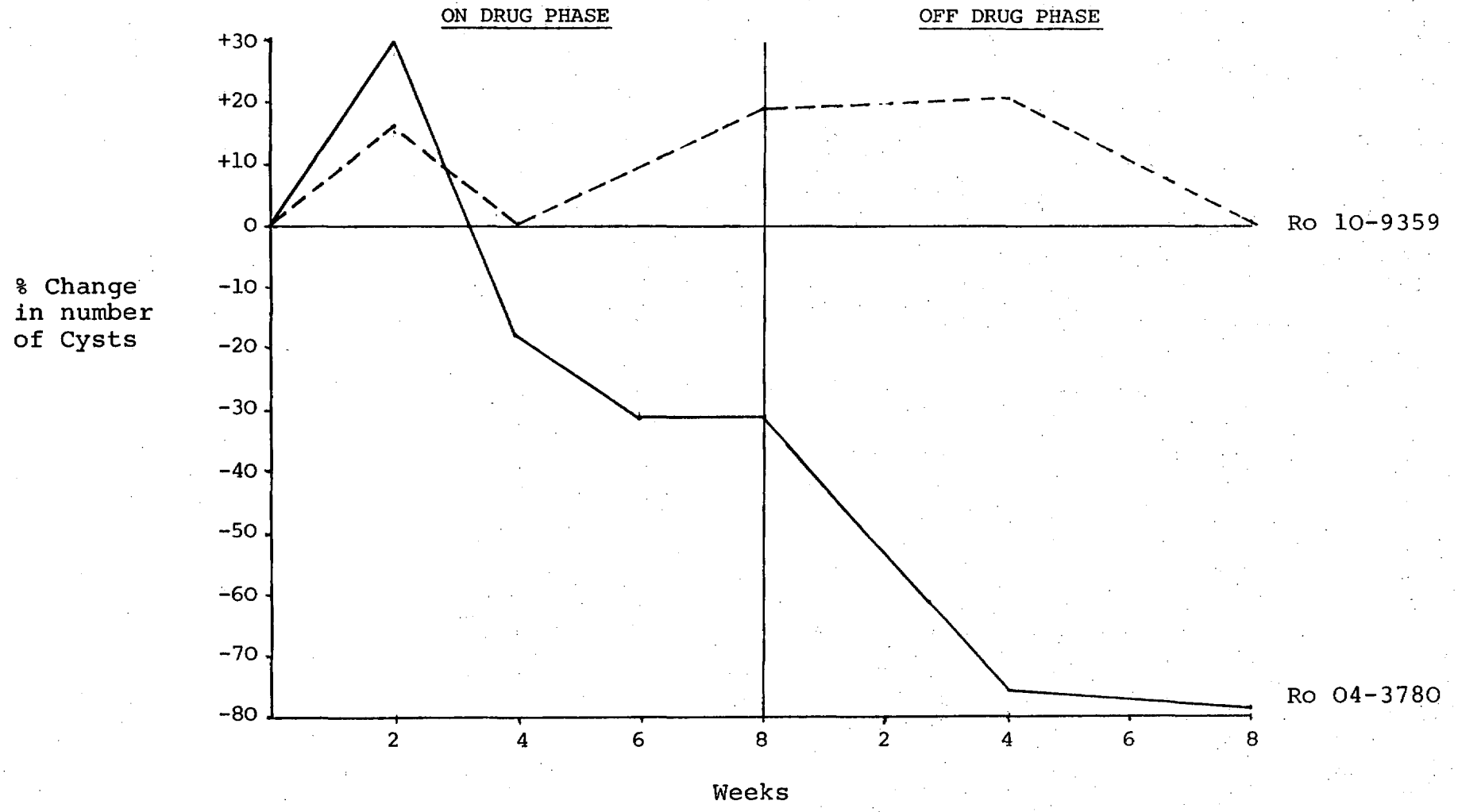
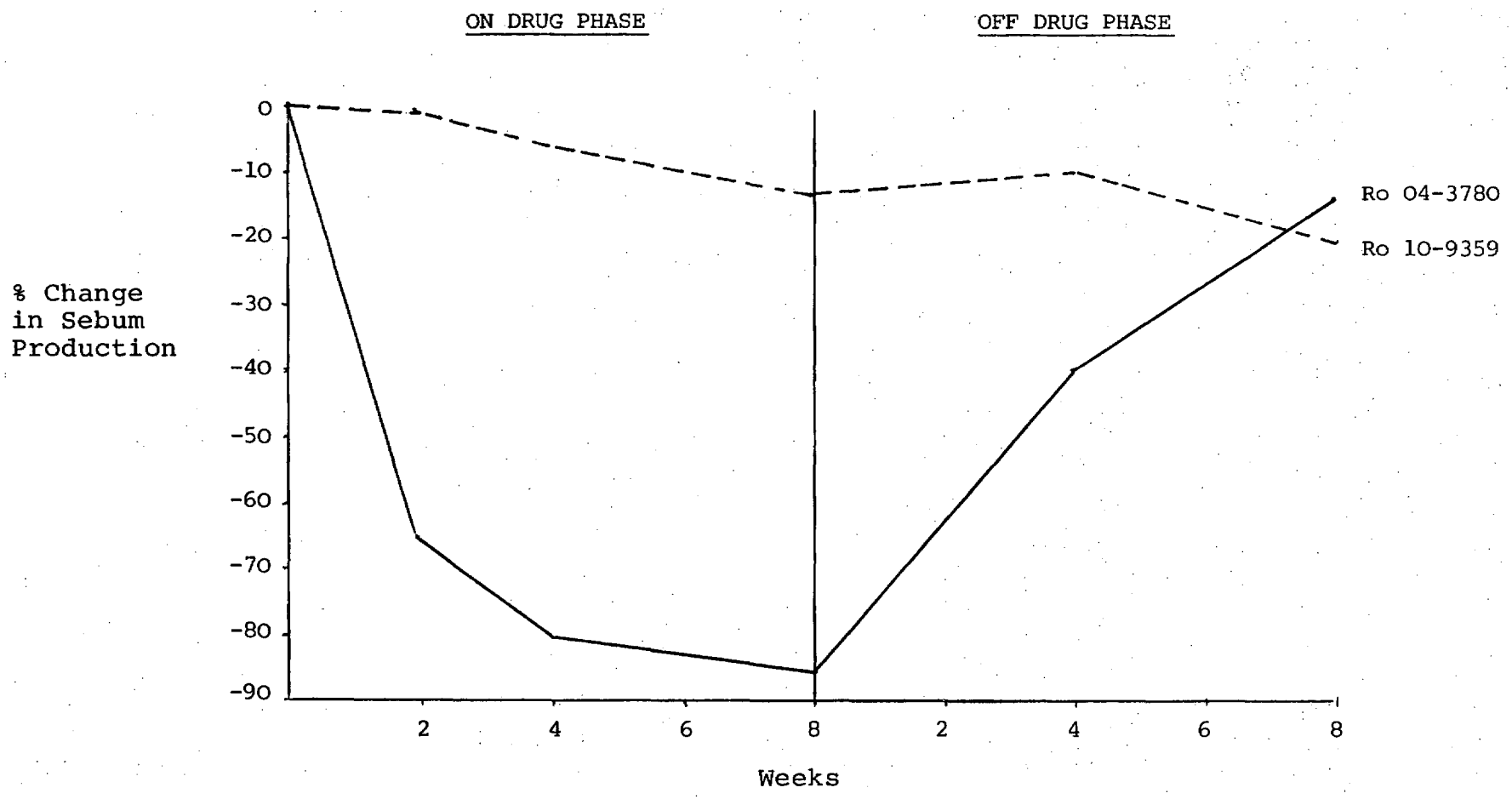


FIGURE 2

% Change in Sebum Production in Both Treatment Groups



Reduction in sebum production in the ROACCUTANE group occurred immediately on starting therapy. The clinical effect on cyst count followed somewhat later. On cessation of treatment the sebum production immediately increased whereas the clinical improvement on cyst count continued during the eight-week off-drug period.

The effect of TIGASON on sebum production was far less evident and the clinical effect on cyst count was minimal.

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 a probable adverse experience.

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

Symptoms, except 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 11.

Table 11/

TABLE 11

Incidence of adverse events on ROACCUTANE and TIGASON

	ROACCUTANE		TIGASON	
Organ System	No Pts	%	No Pts	%
Integumentary	8	100	8	100
Rash	3	38	3	38
Pruritus	5	63	3	38
Sunburn	2	25	2	25
Dry Skin	8	100	5	63
Peeling	1	13	1	13
Bruising	1	13		
Finger tip peeling	3	38	5	63
Cheilitis	8	100	6	75
Fragility of skin	3	38		
Facial dermatitis	4	50	1	13
Hair loss	3	38	4	50
Respiratory	6	75	5	63
Dry nose	5	63	4	50
Epistaxis	3	38	3	38
Musculo-skeletal	3	38	1	13
Joint pain	2	25		
Muscle cramp	1	13	1	13
Gastro-intestinal	4	50	3	38
Soreness of mouth	2	25		
Thirst	1	13	1	13
Abdominal pain	2	25	2	25
Central nervous system	3	38		
Headache	1	13		
Insomnia	2	25		
Special senses	6	75	3	38
Pain in the eyes	1	13		
Irritation	6	75	3	38
Miscellaneous	2	25		
Lethargy	2	25		

All patients were affected, in both treatment groups, by minor and clinically inconsequential symptoms. Cheilitis affected all on ROACCUTANE and 75% of those on TIGASON. The skin and mucous membranes were affected in all patients on either retinoid.

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 bloood 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 12 shows the number and percentage of patients who had laboratory abnormalities classified as probably or possibly drug related.

TABLE 12

Number of patients and percentage with laboratory abnormalities

Organ System - high or low value		ROACCUTANE		TIGASON	
		No Pts	%	No Pts	%
Haematologic		3	37.5	4	50
WBC	high	1	13		
Neutrophils	high	1	13		
Monocytes	high			1	13
ESR		2	26	1	13
Hb	low			1	13
Hepatic		4	50		
Alkaline phosphatase	high	1	13		
SGOT	high	2	25	1	13
SGPT		1	13	1	13
Protein total	high	1	13	3	38
HDL	low	1	13	1	13
Miscellaneous chemistries					
Uric acid	high	5		1	13
Number of patients with adverse experiences		5	63	7	88

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

ROACCUTANE

Patient [redacted] at the end of therapy, with no follow-up baseline or other values available, had a low high-density lipoprotein level of 27mg/dl (normal range 35-70).

Patient [redacted] during therapy with no follow-up evaluations available, had an ESR of 63mm/h.

Patient [redacted] had elevated SGOT and SGPT levels during therapy. SGOT was 19 units at baseline (normal range 7-40 units) and 56 and 43 units at 2 and 4 weeks on therapy, respectively. SGPT was 13 units at baseline (normal range 0-35 units) and 64 and 42 units at 2 and 4 weeks of therapy, respectively.

TIGASON

Patient [redacted], at the end of therapy had an elevated SGOT of 50 units (normal range 7-40) with a normal baseline at two follow-up evaluations.

His SGPT, which was also elevated at the end of therapy (80 units; (normal range 0-35), was 45 units at 2 months follow-up and returned to normal at 4 months follow-up (34 units). His baseline evaluation was within normal range.

Patient [redacted] had low levels of high-density lipoprotein at end of therapy and at 4 months follow-up of 31mg/dl and 27mg/dl, respectively (normal range 35-70). No previous or later data available.

None of these laboratory abnormalities with either retinoid caused the investigator to comment or required a patient to discontinue therapy.

Special tests

Ophthalmologic examination

Patient [redacted] and [redacted] had slight infection of conjunctiva whilst on ROACCUTANE which had not been noticed at baseline.

Patients [redacted] and [redacted] on TIGASON both had raised intraocular tension readings of 25mHg OU (baseline 8mHg OU) and 16mHg, respectively. The follow-up readings of the latter patient returned to 8mHg.

Semen analyses

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

2.3.9 Conclusion and Comment

This study demonstrates that ROACCUTANE at 1mg/kg/day is an effective and safe treatment of cystic acne. TIGASON has been shown to be statistically significantly less effective in the treatment of cystic acne.

The statistically significant fall in cyst count during and for eight weeks after treatment with ROACCUTANE was preceded by an immediate and highly significant fall in sebum production. On cessation of therapy sebum production returned to baseline levels whilst the clinical improvement continued. These parallel events and their time relationship agree with current theories on the role of increased sebum production in the pathogenesis of acne.

The mucocutaneous adverse reactions were well tolerated by the patients in both groups and the laboratory abnormalities did not appear to be of clinical importance.

2.3 SUMMARY OF INDIVIDUAL CLINICAL TRIAL IN ACNE

[redacted]

Redacted under Section 40 of the FOIA.

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	11	10
Male	11	10
Female	0	0
Mean age (yrs)	22.4	26.7
Range	18 - 29	[redacted]
Mean Duration of Disease (yrs)	8.6	13.3
Range	4.2 - 17.8	5.8 - 25.9

Redacted under Section 40 of the FOIA.

There was no difference in sex or age distribution between the two groups. The TIGASON group had cystic acne of longer duration than the ROACCUTANE 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 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 exacerbated by the superimposition of symptoms of hypervitaminosis A.
5. Dietary variation resulting in excessive intake (greater than 50,000 i.u./day of Vitamin A).

Redacted under Section 40 of the FOIA.

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. Redacted under Section 40 of the FOIA.

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

11 patients received ROACCUTANE

10 patients received TIGASON

One patient (no [redacted] who had received TIGASON (etretinate) was lost to follow up after completing the eight-week treatment period.

Medication with ROACCUTANE (isotretinoin) was temporarily discontinued for patient [redacted] due to an intercurrent urinary tract infection. After eight days ROACCUTANE was restarted.

All other patients completed the protocol as designed.

2.3.4 Daily Dosage

The mean daily dose in both groups is shown in Table 2.

TABLE 2

Mean Daily Dosage mg/kg

	ROACCUTANE	TIGASON
Mean	0.99	1.01
±SEM	0.03	0.04
Range	0.95-1.03	0.91-1.05

2.3.5 Duration of Dosage

The duration of therapy is shown in Table 3.

TABLE 3

Duration of Therapy (days)

	ROACCUTANE	TIGASON
Mean	56.4	58.7
±SD	1.1	4.8
Range	55 - 59	55 - 71

There was an eight-week off-drug follow-up period.

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 4 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 4/

TABLE 4

Mean total cyst count

Week	ROACCUTANE Cysts	ROACCUTANE % Change	ROACCUTANE No. Pts	TIGASON Cysts	TIGASON % Change	TIGASON No. Pts	p‡
Baseline	53.6 ±13.4		11	42.9 ±9.6		10	0.737
2 weeks	61.2 ±13.6	+14	11	53.7 ±15	+25	10	0.378
4 weeks	53.1 ±12	-0.9	11	46.3 ±14.4	+7	10	0.382
8 weeks	35.7 ±11.5	-33*	11	41.7 ±11.6	-3	10	0.086
4 weeks off drug	26.2 ±8.3	-51	11	23.1 ±7.5	-48.5	9	0.340
8 weeks off drug	18.6 ±6.2	-65*	11	19.2 ±7.6	-57*	9	0.246

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

‡ Two-sample t-test comparison of treatment changes

At eight weeks of treatment there was a 33% decrease in the number of cysts in the ROACCUTANE group. This within-group difference from baseline was statistically significant ($p < 0.05$). The difference between the groups at the end of treatment was clinically significant but did not reach statistical significance, $p = 0.086$.

After eight weeks off drug, further improvement from baseline was noticed with both drugs, ROACCUTANE having achieved a 65% decrease and TIGASON a 57% decrease in total number of cysts. Both these within-group results were statistically significant ($p < 0.05$).

Cyst Count - Face

Table 5 shows the mean cyst count on the face before, during and after eight weeks' treatment and during eight weeks' follow-up off this drug.

TABLE 5

Mean Facial Cyst Count ±SE

	ROACCUTANE			TIGASON			
Week	Cysts	% Change	No. Pts	Cysts	% Change	No. Pts	p‡
Baseline	4.6 ±1.5		11	2.7 ±1.2		10	0.834
2 weeks	6.8 ±1.9	+47	11	3.7 ±1.7	+37	10	0.781
4 weeks	3.3 ±1.2	-29	11	2.7 ±1.2	0	10	0.189
8 weeks	1.6 ±0.6	-67*	11	4 ±1.4	+48	10	0.027
4 weeks off drug	1.3 ±0.6	-73*	11	1.9 ±1.2	-23	9	0.036
8 weeks off drug	0.6 ±0.4	-88*	11	1.7 ±0.8	-32	9	0.041

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

‡ Two-sample t-test comparison of treatment changes.

At eight weeks there was a 67% decrease in the cyst count of the face in the ROACCUTANE group. This within-group change from baseline was significant ($p < 0.05$). Statistically significant decreases of 73% and 88% were also seen in the ROACCUTANE group at four and eight weeks off drug.

The difference between the ROACCUTANE and the TIGASON at eight weeks was clinically and statistically significant, $p = 0.027$, with ROACCUTANE giving the better results. This superior effect of ROACCUTANE was also seen on the face at four and eight weeks off drug ($p = 0.036$, 0.041 respectively).

Cyst Count - Back

Within the Ro 04-3780 group, a 30% decrease from baseline in cyst count on the back at eight weeks; 47% decrease at four weeks off drug; and 61% decrease at eight weeks off drug reached statistical significance, $p < 0.05$. Within the TIGASON group a 49% decrease at four weeks and a 64% decrease at eight weeks off drug reached statistical significance, $p < 0.05$.

Cyst Count - Chest

In the ROACCUTANE group the improvement in the chest area at eight weeks was 31% but this did not reach the $p < 0.05$ level of significance. At four and eight weeks off drug, however, the 53% and 68% respective decreases from baseline were statistically significant at $p < 0.05$ level. In the TIGASON group there were no similar significant decreases in the chest regions.

The change in mean number of cysts for all areas after eight weeks of treatment are summarised in Table 6.

TABLE 6

Change in mean number of cysts at eight weeks + SEM

Area	ROACCUTANE	% Change	TIGASON	% Change	p‡
Total	-17.8	-33*	-1.2	-3	0.086
±	8.0		8.6		
Face	-3.1	-67*	+1.3	+48	0.027
±	1.4		1.6		
Chest	-4.6	-30	-1.2	-9	0.285
±	3.3		4.8		
Back	-10.2	-30*	-1.3	-5	0.125
±	5.4		5.1		

‡ Two-sample t-test comparison of treatment changes.

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

In both groups at two weeks there was an initial worsening of their cystic acne.

Patients' and Physician's Global Evaluations

Table 7 shows the mean subjective scores at eight weeks from baseline in both groups of patients as assessed by the Physician.

TABLE 7

Mean Subjective Score Physician's Global Evaluation

	ROACCUTANE	±SEM	TIGASON	±SEM	p*
8 weeks	+ 1.36	0.36	0	0.49	0.02

* 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

At eight weeks patients treated with ROACCUTANE achieved a score indicating minimal to definite improvement whereas TIGASON patients showed no change. This difference between the two groups is statistically significant.

Table 8 shows a similar result in the patients' own assessment of response.

TABLE 8

Mean subjective Score ±SEM Patients' Global Evaluation

	ROACCUTANE ±SEM	TIGASON ±SEM	p
8 weeks	+1.36 0.39	0.2 0.49	0.04

Table 9/

TABLE 9

Number of patients achieving different levels of improvement at eight weeks.

ROACCUTANE			TIGASON		
Worse	No Change	Better	Worse	No Change	Better
1	3	7*	3	5	2

* The probability of this distribution of responses is <0.05.

Sebum Production

The change in sebum production during the trial in both groups is shown in Table 10.

TABLE 10

Mean sebum production (mg/10cm^2/3hr)

	ROACCUTANE			TIGASON			
	Sebum ±SE	% Change	No. Pts	Sebum ±SE	% Change	No. Pts	p‡
Baseline	4.4 0.3		11	5.1 0.4		10	0.08
Week 2	1.6 0.3	-63	11	4.8 0.3	-5	10	0.000
Week 4	0.8 0.1	-82	11	4.6 0.4	-10	10	0.000
Week 8	0.6 0.1	-87	11	4.8 0.4	-5	10	0.000

‡ Two sample t-test comparison.

In the ROACCUTANE group there was an immediate drop of 63% in sebum production at two weeks and continuing falls of 82% at four weeks and 87% at the end of treatment. All these within-group changes were significant statistically at the $p < 0.05$ level.

There was no change in the TIGASON group throughout the trial or during the eight-week off-drug follow-up.

This difference in change of sebum production between the two groups is very marked clinically and significant statistically at the $p < 0.05$ level at every assessment during the eight-week trial.

At four and eight weeks off drug the percentage decreases of sebum production in the ROACCUTANE group were 42% and 24%, respectively. Both these differences from baseline were statistically significant at the $p < 0.05$ level. At four weeks off drug the difference between the two groups was statistically significant ($p = 0.007$, one-sided probability), with ROACCUTANE giving the better result. At eight weeks off drug statistical significance was lost.

Figures 1 and 2 show the changes of total cyst count and sebum production in the two groups of patients.

Figures 1 and 2/

FIGURE 1

Change in Total Number of Cysts

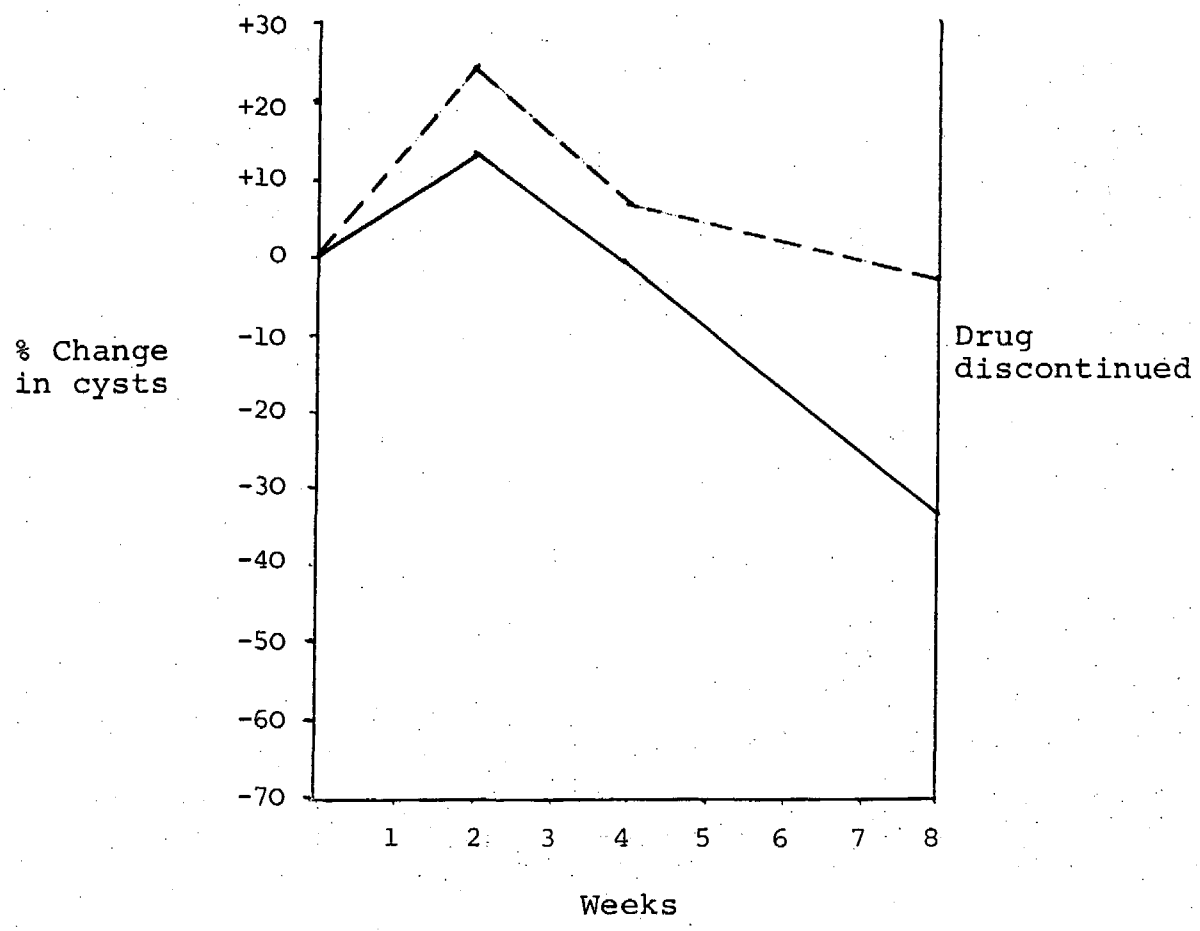
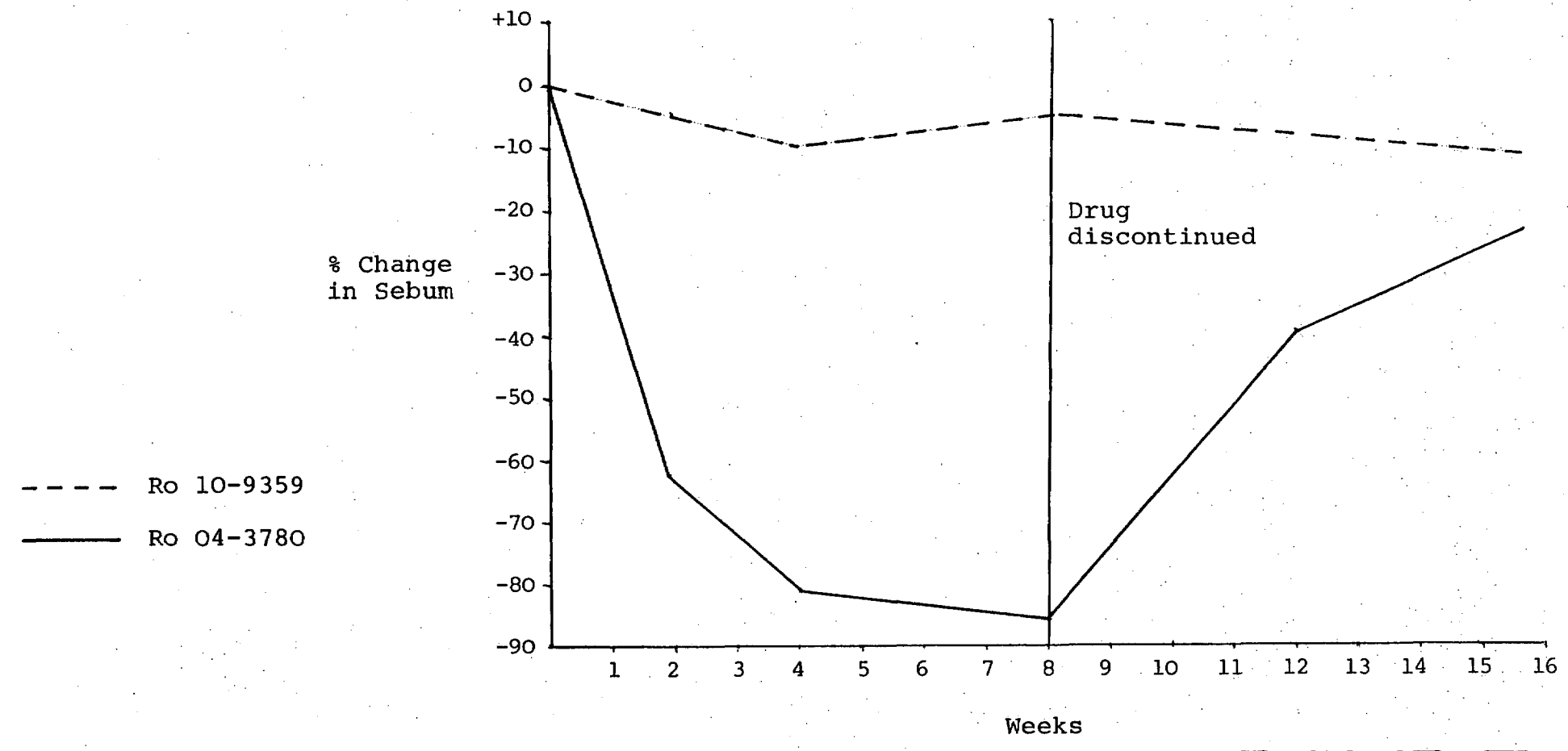


FIGURE 2

Change in Sebum Production



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 a probable adverse experience.

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

Symptoms, except 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 11.

Table 11/

TABLE 11

Incidence of adverse events on ROACCUTANE and TIGASON

	ROACCUTANE		TIGASON	
Organ System	No Pts	%	No Pts	%
Integumentary	**11**	**100**	**10**	**100**
Rash	5	46	4	40
Pruritus	8	73	6	60
Sunburn	0	0	1	10
Dry Skin	11	100	7	70
Peeling	1	9	9	90
Finger tip peeling	2	18	7	70
Cheilitis	11	100	10	100
Fragility of skin	7	64	4	40
Facial dermatitis	10	91	2	20
Hair loss	2	18	7	70
Respiratory	**9**	**82**	**6**	**60**
Dry nose	8	73	6	60
Sore throat	1	9	0	0
Epistaxis	6	55	3	30
Musculo-skeletal	**1**	**9**	**0**	**0**
Joint pain	1	9	0	0
Gastro-intestinal	**7**	**64**	**7**	**70**
Soreness of mouth	5	46	4	40
Nausea	0	0	1	10
Increased appetite	1	9	0	0
Anorexia	1	9	2	20
Thirst	1	9	3	30
Pruritus ani	0	0	1	10
Central nervous system	**3**	**27**	**3**	**30**
Headache	3	27	1	10
Insomnia	2	18	3	30
Special sensory	**7**	**64**	**1**	**10**
Blurred vision	0	0	1	10
Diploplia	0	0	1	10
Pain in the eyes	3	27	0	0
Irritation of eyes	5	46	0	0
Miscellaneous	**2**	**18**	**4**	**40**
Lethargy	1	9	4	40
Fever	1	9	1	10

The integument was affected in all patients in both groups. Cheilitis was noticed in all patients and other mucocutaneous areas were affected frequently including the nasal mucous membrane in 73% and 60% of the ROACCUTANE and TIGASON groups, respectively. Drying of the skin affected 100% of the ROACCUTANE and 70% of the TIGASON patients.

There were differences in the incidence of adverse reactions in the two groups. 90% of the TIGASON patients suffered peeling of the skin as opposed to 9% of the ROACCUTANE patients, and 91% of the ROACCUTANE patients had a facial dermatitis whereas only 20% of the TIGASON patients were affected. Again there was pain and irritation of the eyes (27% and 46%) in the ROACCUTANE group and none in the TIGASON group.

In no instance was the dosage of drug reduced or a patient removed from the study due to a drug-related clinical symptom.

Laboratory investigations

Data obtained

The following routine blood and urine studies were obtained at baseline and 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 12 shows the number and percentage of patients who had laboratory abnormalities classified as probably or possibly drug related.

Table 12/

TABLE 12

Number of patients and percentage with laboratory abnormalities

Organ System - high or low value		ROACCUTANE No Pts	ROACCUTANE %	TIGASON No Pts	TIGASON %
Haematologic		**0**	**0**	**1**	**10**
WBC - high		0	0	1	10
Hepatic		**3**	**27**	**4**	**40**
SGPT	high	1	9		
GGPT	high	1	9		
Alkaline phosphatase	high			2	20
Bilirubin	high			1	10
Albumin	high	1	9		
Globulin	high			1	10
Total protein		2	18		
Electrolytes		1	9	1	10
Sodium	low	1	9		
Chloride	low			1	10
Miscellaneous chemistries		**4**	**36**	**5**	**50**
Fasting blood sugar	high			1	10
Calcium	high	1	9		
Phosphorus	low			2	20
Uric acid	high	2	18	2	20
Cholesterol	high			1	10
Trigylcerides	high	2	18	2	20
Urinary		**5**	**46**	**4**	**40**
wbc in urine		1	9	2	20
Epithelial cels in urine		3	27		
Bacteria in urine		2	18		
Calcium oxalate crystals		2	18	2	20
Acetone				1	10
Number of patients with adverse experiences		9	82	7	70

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

ROACCUTANE

Patient [redacted] at the end of therapy showed an elevation of triglycerides 224mg/dl, with no follow-up data.

Patient [redacted] had an elevated uric acid level (8.4mg/dl), patient [redacted] had 10 wbc/hpf in his urine, patient [redacted] had an elevated SGPT (86 units). These abnormalities occurred at the end of therapy with previously normal values and no follow-up data.

Patient [redacted] had a consistently elevated level of GGPT > 80 units during therapy. He also had an elevated SGPT 120 units prior to starting therapy and it remained consistently elevated during treatment. There was a prior history of moderate alcohol intake which was reduced at the start of therapy. During therapy he had elevated triglycerides (to 317 mg/dl) which returned to normal before therapy was discontinued.

TIGASON

At the end of therapy, with no follow-up data available, the following abnormalities were found:

Patient [redacted] had 10 wbc/hpf in the urine and lowered serum phosphorus (1.9 mg/dl).

Patient [redacted] had an elevated uric acid (8.6 mg/dl).

Patient [redacted] showed isolated abnormalities, after he had been off the drug for six days:10 wbc/hpf in urine, bilirubin level 2.27 mg/dl, chloride 95 mmol/l, fasting blood sugar 159 mg/dl. There were no abnormalities during therapy.

Patient [redacted] had an elevated triglyceride (to 221 mg/dl) after seven days off drug.

During treatment patient 09 had a consistently elevated wbc (to 15600/cmm). No follow-up data were available. Patient [redacted] had elevated triglyceride levels (to 206 mg/dl) which returned to normal whilst he was still on drug therapy.

The only abnormalities which the investigator felt to be worthy of comment were those affecting the liver function tests of patient [redacted]. Even so they were not thought to be sufficient to require the patient to stop therapy.

Special tests

Baseline and follow up ophthalmologic examination and semen analyses were performed on all patients:-

Ophthalmologic examination

Patient [redacted] developed seborrhoeic blepharitis and follicular changes during therapy with ROACCUTANE.

Patient [redacted], on TIGASON, showed a mild conjunctival infection and lash debris.

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 the efficacy of ROACCUTANE in treating cystic acne and its statistically significant superiority over TIGASON. The incidences of clinical and laboratory adverse reactions with the two retinoids are similar although there are some differences.

The mucocutaneous symptoms were well tolerated by the patients and the laboratory abnormalities did not appear to be of clinical importance.

The significant reduction of sebum production whilst on ROACCUTANE preceded clinical improvement.