CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20405

MEDICAL REVIEW(S)

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Joint Clinical Review

NDA: 20-405 Original NDA amendment (digoxin for heart failure).

Sponsor: GlaxoWellcome

Submission date: 17 July 1996 (study protocol); 18 November 1996 (NIH dataset); request for labeling change 7 April 1997.

Reviewers:

W. Nuri, Ph.D.

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Concur:

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1. Submission

The sponsor has submitted the protocol for a single NHLBI-sponsored multi-center study (the DIG trial), a set of blank case report forms, and a collection of SAS datasets. The study report includes a publication[1]. There is no indication of study protocol amendments.

The Division had previously recommended approval of NDA 20-405, largely on the basis of the RADIANCE and PROVED studies. The Cardio-Renal Advisory Committee recommended deferring a decision until the results of the DIG study were available.

2. Protocol

2.1. Source

The summary is based upon a document dated July 1992, entitled "Trial to evaluate the effect of digitalis on mortality in heart failure". The title page indicated this is the "final protocol".

2.2. Objectives

The primary objective was to determine the effect of digitalis on all-cause mortality in subjects with clinical heart failure and ejection fraction ≤0.45. Secondary objectives were to look for effects on hospitalizations for heart failure, cardiovascular mortality, heart failure mortality, death plus hospitalization for heart failure in subjects with ejection fraction >0.45, hospitalization for non-cardiovascular causes, and quality of life.

It was also prospectively planned to look at subgroups based upon ejection fraction, heart size on chest x-ray, etiology of heart failure, prior use of digoxin, and NYHA class.

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[1] The Digitalis Investigation Group. 1997. The effect of digoxin on mortality and morbidity in patients with heart failure. *New Eng. J. Med.* 336(8):525-533.

The section of the protocol detailing compensation to investigators refers to quality of life and 6-minute walk test sub-studies which are not otherwise described in the protocol.

2.3. Eligibility

Subjects could be any NYHA class. The diagnosis of heart failure was based upon evidence of low cardiac output (including limitations in activity) or congestion (edema, elevated JVP, rales, or radiologic evidence of pulmonary congestion). Subjects with ejection fraction ≤0.45 entered the main study, while those with ejection fraction >0.45 entered a separate study. Exclusion criteria were (1) age <21 years, (2) no baseline ejection fraction, (3) myocardial infarction, cardiac surgery, or PTCA within 4 weeks, (4) unstable or refractory angina within 1 month, (5) second or third degree AV-block without a pacemaker, (6) atrial fibrillation or atrial flutter, (7) cor pulmonale, (8) uncorrected constrictive pericarditis, (9) acute myocarditis, (10) hypertrophic cardiomyopathy, (11) amyloid cardiomyopathy, (12) complex congenital heart disease, (13) pre-excitation syndrome, (14) current need for intravenous inotropes, (15) potassium outside 3.2 to 5.5 mM, (16) immediate need for cardiac surgery or candidacy for heart transplantation, (17) sick sinus syndrome without pacemaker, (18) non-cardiac causes of heart failure, (19) creatinine >3 mg/dL or severe hepatic disease, (20) non-cardiac disease causing life expectancy <3 years, and (21) chronic alcoholism or social factors apt to influence adherence to the protocol.

2.4. Study procedures

2.4.1. Pre-randomization

Prior to randomization, subjects were to be clinically stable for at least 2 weeks. Subjects not on ACE inhibitors and having no contraindications were to be placed on ACE inhibitor.

The baseline ejection fraction measurement could be within 6 months of randomization, by radionuclide angiography, contrast angiography, or 2-D echocardiography, but not within 7 days of myocardial infarction, cardiac surgery, or PTCA.

2.4.2. Randomization

Baseline data were to be provided to the Data Coordinating Center, which then issued the randomization number. There is no indication whether baseline data were used for stratification.

2.4.3. Follow-up

The first scheduled follow-up visit was at 4 weeks. Subsequent follow-up visits were at 4-month intervals. Subjects were to be followed until the last enrolled subject had been followed for 2 years.

2.4.4. Dosing

Study drug was available as 0.125, 0.25, 0.375, or 0.5 mg/day. The initial dose of study drug or matching placebo was recommended by the Data Coordinating Center at randomization, based upon age, gender, weight, and serum creatinine, but investigators were free to adjust based upon other factors, including the previous dose of digoxin or concomitant medications.

Blood levels of digoxin were ascertained at a central laboratory at the initial follow-up visit (4 weeks). Investigators were discouraged from performing other digoxin-level assessments except in life-threatening circumstances. Subjects in whom unblinding became necessary were to continue in the study.

Study drug was to be maintained, as far as possible, through intercurrent events. Worsening heart failure was to be treated with adjustments to concomitant medications. If that was not sufficient, subjects could be discontinued from blinded drug and begun on open-label digoxin. Study drug could also be interrupted for myocardial infarction. For suspected digoxin-related arrhythmias, subjects could have the dose decreased or interrupted while maintaining the blind, or they could be discontinued from blinded treatment and begun on open-label digoxin.

Five hundred subjects (250 on digoxin) had blood samples collected at 4 weeks and 1 year for assessment of digoxin levels by the central laboratory. These data were collected to test whether, in a population-sense, subjects were receiving doses that put their digoxin levels in the therapeutic range[2].

Where a blinded assessment of digoxin level was requested from the Central Laboratory, such results were to be reported categorically as "probably toxic", "therapeutic or possibly toxic", or "subtherapeutic", with placebo group results always reported in the latter category.

2.4.5. Statistical plan

Historical data were used to estimate the baseline mortality rate (27% on placebo), need for open-label digoxin (15% over 3 years), and compliance (85% at 3 years). The trial, with 3500 subjects per treatment group, was sized to detect, with 90% power, a 15% treatment effect on mortality with a two-tailed α=0.05.

The primary end point was an intent-to-treat analysis of all-cause mortality for the full duration of study. Analysis was to be by Kaplan-Meier survival curves and a log-rank test.

The DSMB was to decide on stopping rules. There is no indication in the protocol how often data were to be provided to the DSMB or how often the DSMB would meet.

Subgroup hypotheses were to be tested by 'tests of interaction'; significance of subgroup comparisons was to be assessed after Bonferroni adjustment. No p-values were to be assigned to data-derived subgroup analyses.

2.4.6. Organization

The protocol and the resulting publication are attributed to the Digitalis Investigation Group (DIG). The study was managed through the Project Office of the Clinical Trials Branch of the NHLBI. There was a Steering Committee comprised of 11 academic investigators in 10 institutions in the US and Canada. The Data Coordinating Center was in the Cooperative Studies Program Coordinating Center of the VA Medical Center in Perry Point, MD. The Pharmacy Coordinating Center was in the Cooperative Studies Program Clinical Research Pharmacy Coordinating Center of the VA Medical Center in Albuquerque, NM.

The Data and Safety Monitoring Board consisted of 7 individuals at academic institutions in the US and Canada. The DSMB could recommend changes based upon events in blinded data.

The study was planned for 200 centers in the US and Canada.

3. Results

3.1. Source data

Except where noted, information presented here came from analyses of SAS datasets provided by the sponsor. In these datasets, the only apparent way to distinguish to which trial subjects belong is by examination of the baseline ejection fraction. These values give the same distribution of subjects in the two placebo groups as is indicated in the publication, but it shifts one subject on digoxin from the EF>0.45 trial to the EF≤0.45 trial.

3.2. Demographics

Three hundred and one centers enrolled 0 to 206 subjects with EF≤0.45 and 0 to 78 subjects with EF>0.45. Table 1 below shows demographic characteristics of randomized subjects. As expected from a study of this size, the treatment groups were very well matched. The mean age was >60 years, most heart failure was of ischemic etiology, and most subjects had a history of myocardial infarction. About 45% of subjects were on digoxin within 1 week of randomization, 79% were on diuretics, and 95% were on ACE inhibitor. Blacks and women were reasonably represented.

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[2] Apparently the Data and Safety Monitoring Board recommended this be amended to include digoxin, potassium, creatinine, and magnesium levels measured in all subjects at 4 weeks and 1 year. Potassium and creatinine levels were also to be ascertained at the beginning of any hospitalization for suspected digoxin toxicity.

Table 1. Demographic and baseline characteristics of randomized subjects.

	EF≤0.45		EF>0.45	
	Placebo N=3403	Digoxin N=3398	Placebo N=496	Digoxin N=491
Male (%)	77.5	77.8	59.7	57.8
Caucasian (%)	85.2	85.7	86.7	85.5
Black (%)	11.6	11.7	10.3	11.4
Other (%)	3.2	2.7	3.0	3.1
CHF etiology (%)				
Ischemic	71	71	57	57
Hypertensive	9.1	8.1	21	24
Valvular	1.5	1.4	8.3	6.3
HR ($\bar{x}$±SD)	79±13	79±13	77±12	75±12
SBP ($\bar{x}$±SD)	126±20	126±20	137±21	138±21
DBP ($\bar{x}$±SD)	75±11	75±11	77±11	77±12
CHF Sx <1 mo (%)				
Rales	17	17	16	16
Increased JVP	14	14	7.6	8.8
Peripheral edema	20	20	27	27
Dyspnea at rest	23	22	20	20
History of (%)				
Myocard infarct	65	65	49	50
Current angina	26	27	29	30
Diabetes mellitus	29	28	30	27
Hypertension	46	45	58	62
On digoxin	45	44	36	34
Digoxin—recomm				
0.000 mg (%)	0.2	0.1	0.6	0.0
0.125 mg (%)	5.7	5.5	7.1	7.1
0.250 mg (%)	77	77	77	76
0.375 mg (%)	16	15	13	15
0.500 mg (%)	1.6	2.1	2.2	1.6

	EF≤0.45		EF>0.45	
	Placebo N=3403	Digoxin N=3398	Placebo N=496	Digoxin N=491
Age ($\bar{x}$±SD)[a]	64±11	63±11	—	—
EF ($\bar{x}$±SD)	28±9	29±9	55±8	55±8
CT ratio ($\bar{x}$±SD)	0.53±0.07	0.53±0.07	0.52±0.07	0.52±0.08
CHF Hx, mo ($\bar{x}$±SD)	30±37	31±37	29±36	25±30
CHF etiology (%)				
Idiopathic	14	15	11	10
Alcoholic	3.8	2.7	1.4	1.2
Other	1.2	2.1	1.6	1.4
NYHA I (%)	13	14	21	19
NYHA II (%)	55	53	57	59
NYHA III (%)	31	31	21	21
NYHA IV (%)	1.9	2.2	1.6	0.8
CHF Sx <1 mo (%)				
Dyspn on exertion	76	75	75	71
Limited activity	77	76	71	71
S_3	25	27	8.2	13
Pulm congestion	15	15	11	10
History of (%)				
On K-sparing diur	8.2	7.0	8.3	7.7
On other diuretic	79	78	77	75
On ACE inhibitor	95	94	86	86
On nitrates	43	42	39	39
On hydralazine	1.9	2.3	1.2	2.2
On K supplement	32	31	30	30
Digoxin—actual				
<0.125 mg (%)	0.4	0.5	0.6	0.2
0.125 mg (%)	17	18	22	22
0.250 mg (%)	70	71	68	67
0.375 mg (%)	11	10	7.7	10
0.500 mg (%)	0.9	1.1	1.4	0.6

a. Age information is not recorded in the dataset corresponding to the baseline visit, so these values are from the publication.

3.3. Protocol adherence

Investigators rated subjects categorically for taking study drug at each visit. Ninety to 93% of subjects in each treatment group were at least 80% compliant at the first visit and then 80% compliance rates gradually fell to 70 to 80% at the longest times of follow-up, with no systematic differences between placebo and active groups or for subjects with EF≤0.45 or EF>0.45. Doses at each visit averaged 0.21 to 0.27 mg on placebo and 0.21 to 0.23 mg on digoxin among subjects with EF≤0.45, and 0.22 to 0.25 mg on placebo or digoxin among subjects with EF>0.45.

The protocol was intended to achieve specific goals with respect to digoxin levels—0.5 to 2.0 ng/mL. Digoxin levels were collected from about half of the subjects in both groups, but few of the placebo group samples were analyzed. According to the publication, digoxin levels in the active treatment group measured at least 6 hours after dosing averaged 0.86 ng/mL at 1 month, with 88% of subjects within the target range, and 0.80 ng/mL after 12 months. At the 1-month visit, subjects on digoxin 0.125 mg had digoxin levels averaging 0.76 ng/mL, while those on doses of 0.25, 0.375, or 0.5 mg had digoxin levels averaging 0.88 to 0.89 ng/mL.

Ninety-four to 96% of subjects remained on randomized study drug after the first (1-month) visit. The fraction of subjects on randomized treatment fell during the study, to 70 to 79%, after 4 years, with no systematic differences between placebo and active groups or for subjects with EF≤0.45 or EF>0.45. Reasons for discontinuing study drug

were categorized by the investigator as side effects (5 to 7% on placebo, 10 to 13% on digoxin), renal insufficiency (2 to 3% on placebo, 2 to 7% on digoxin), need for open-label digoxin to treat CHF (17 to 39% on placebo, 13 to 24% on digoxin), need for open-label digoxin to treat atrial fibrillation (12 to 30% on placebo, 9 to 11% on digoxin), and 'other' (42 to 47% on placebo, 52 to 58% on digoxin).

3.4. Follow-up

Figure 1 below shows, for EF≤0.45 and EF>0.45 and by treatment group, the extent of follow-up. In this analysis, subjects who died have a known status from that point onward and are counted as being followed indefinitely, i.e., the curves are 'survival analyses' for being alive and being followed or being dead. Follow-up was similar in both treatment groups (the treatment group curves are virtually indistinguishable in Figure 1) and the difference between the two studies is a result of the difference in mortality.

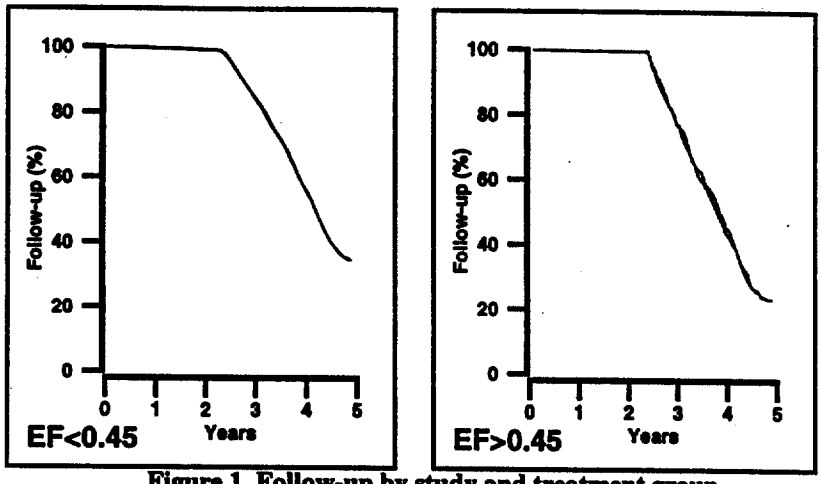

Figure 1. Follow-up by study and treatment group.

3.5. Pre-specified end points

The Kaplan-Meier procedure was used to estimate the survival distributions. Relative risk for survival was estimated using the Cox proportional hazards model. Wilcoxon rank-sum test was used to compare counts of events. Subjects could have more than one hospitalization, and the protocol did not specify whether the analyses should be by counts of events or subjects with events. The results of analyses of protocol-specified end points are shown in Table 2 below.

Table 2. Treatment effects on protocol-specified end points.

All-cause mortality[b]	0.99	0.91-1.07	0.80	0.99	0.76-1.28	>0.05
where C-T ratio ≤0.55	0.99	0.89-1.10	0.91	1.04	0.76-1.44	0.80
where C-T ratio >0.55	0.98	0.86-1.11	0.72	0.88	0.57-1.35	0.55
CHF hospitalization[c]						
Subjects	0.72	0.66-0.79	<0.001	0.82	0.62-1.09	0.18
Events	0.87	0.82-0.92	0.0001	0.76	0.62-0.93	0.008
Cardiovascular mortality[d]	1.01	0.93-1.10	0.78	0.99	0.72-1.34	0.93
CHF mortality[e]	0.88	0.77-1.01	0.06	0.96	0.58-1.60	0.88
Death plus CHF hospitalization[f]	0.85	0.79-0.91	<0.001	0.82	0.63-1.07	>0.05
Non-cardiovascular hospitalization[g]	1.06	0.98-1.15	>0.05	0.97	0.80-1.19	0.80
Quality of life[h]	—	—	—	—	—	—

a. RR (relative risk) defined as risk on digoxin divided by risk on placebo.

b. DIG performed both analyses by EF group only. Reviewers performed protocol-specified analyses by EF and cardio-thoracic ratio.
c. DIG analyzed subjects with EF≤0.45 and reviewers performed other 3 analyses.
d. DIG analyzed subjects with EF≤0.45 and the reviewers analyzed subjects with EF>0.45.
e. DIG analyzed subjects with EF≤0.45 and the reviewers analyzed subjects with EF>0.45.
f. DIG performed both analyses shown. However, only the analysis in subjects with EF>0.45 was protocol-specified.
g. DIG analyzed subjects with EF≤0.45 and the reviewers analyzed subjects with EF>0.45. The reviewers' analysis of subjects with EF≤0.45 produced RR=1.4, 95% CI 0.96-1.13, P=0.31.
h. No analysis of quality of life was presented by DIG and the data were not available for review.

The published version of the all-cause mortality analysis is reproduced in Figure 2 below. Causes of mortality are summarized in Table 3 below[3].

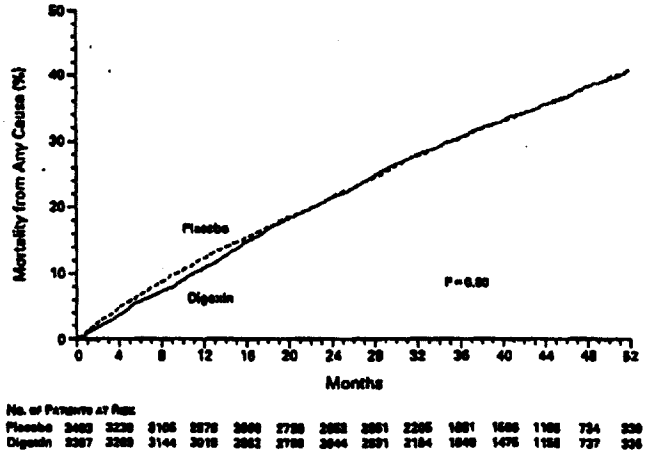

Figure 2. Mortality (EF≤0.45).

Table 3. Causes of death.

	EF≤0.45		EF>0.45	
	Placebo (N=[illegible])	Digoxin (N=[illegible])	Placebo (N=96)	Digoxin (N=91)
Presumed arrhythmia without worsening CHF	259	295	21	14
Progressive heart failure	429	379	30	30
Other cardiac	208	223	21	29
Stroke	27	23	2	5
Embolism	9	12	2	1
Other vascular	12	20	4	1
Non-cardiac, non-vascular	196	168	31	25
Unknown	51	64	5	7
Total	191	[illegible]	116	112

[3] This analysis was performed by the reviewers. The DIG publication gives the total numbers of deaths per group as 1194, 1181, 116, and 115, respectively. The sponsor's analyses for the main study showed 1193 and 1180 deaths on placebo and digoxin, respectively. No effort was made to resolve these minor discrepancies.

All CHF hospitalization analyses shown in Table 2 on page 5 counted events where CHF was the primary reason for hospitalization. For another 20% of hospitalizations, CHF was a contributory cause; the corresponding relative risk was similar.

3.6. Other exploratory analyses

The publication contains the results of numerous analyses of non-protocol-specified cause-specific morbidity and mortality end points. These are neither reviewed nor summarized here.

All-cause hospitalization was analyzed by DIG, the sponsor, and the reviewers. Counts of hospitalization are shown in Table 4 below.

Table 4. All-cause hospitalization.

	Total events				Subjects			
	EF≤0.45		EF>0.45		EF≤0.45		EF>0.45	
	Placebo N=3403	Digoxin N=3398	Placebo N=496	Digoxin N=491	Placebo N=3403	Digoxin N=3398	Placebo N=496	Digoxin N=491
DIG publication	6777	6356	—	—	2282	2184	—	—
Sponsor	6824	6397	—	—	—	—	—	—
Reviewers								
All hospitalizations	6824	6397	962	984	2291	2190	331	332
Not fatal same day	6770	6337	956	979	2274	2163	331	328

Contributory and primary causes for hospitalization were categorized by investigators. Most commonly 2 contributory causes were identified per hospitalization. Table 5 below shows the causes for hospitalizations which were not the same day fatal.

Table 5. Causes for hospitalization.

	EF≤0.45		EF>0.45			EF≤0.45		EF>0.45	
	Placebo N=3403	Dig N=3398	Placebo N=496	Dig N=491		Placebo N=3403	Dig N=3398	Placebo N=496	Dig N=491
Primary causes									
Worsening heart failure	2513	1894	211	168	Stroke	154	146	22	18
Other	1910	1995	388	393	Digoxin toxicity	36	74	3	10
Unstable angina	606	594	82	139	Other cardiovascular surgery	54	74	10	14
Other cardiovascular	596	674	90	94	CABG	60	60	9	8
Respiratory infection	297	294	58	34	PTCA	16	25	6	9
Supraventricular arrhythmia	160	127	37	36	Cardiac transplant	15	23	1	1
Ventricular arrhythmia	162	177	6	11	Valve operation	6	5	5	4
Myocardial infarction	222	221	29	43					

Table 5. Causes for hospitalization. (Continued)

	EF≤0.45		EF>0.45			EF≤0.45		EF>0.45	
	Plcbo N=3403	Dig N=3398	Plcbo N=496	Dig N=491		Plcbo N=3403	Dig N=3398	Plcbo N=496	Dig N=491
Contributory causes									
Worsening heart failure	3025	2313	290	230	Stroke	167	165	29	22
Other	2356	2311	441	451	Digoxin toxicity	94	179	6	27
Unstable angina	848	808	109	170	Other cardiovascular surgery	114	129	15	17
Other cardiovascular	807	886	119	129	CABG	102	90	16	17
Respiratory infection	508	446	79	57	PTCA	39	62	8	10
Supraventricular arrhythmia	398	339	69	74	Cardiac transplant	25	32	1	1
Ventricular arrhythmia	332	353	13	17	Valve operation	12	13	6	5
Myocardial infarction	279	302	36	51					

As shown in Table 2 on page 5, a time to first event analysis of death or hospitalization for worsening heart failure was a prospective end point for which a nominally highly significant treatment effect was observed. The corresponding survival curves, shown in Figure 3 below[4], separate early and the difference is maintained throughout the rest of the period of follow-up.

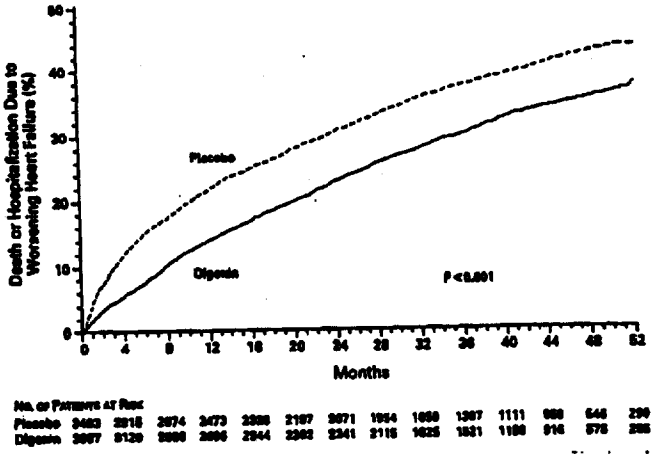

Figure 3. Mortality or hospitalization for worsening heart failure (EF≤0.45).

The time course for the development of treatment effects is protracted, but consistent with the development of treatment effects in the RADIANCE and PROVED digoxin withdrawal trials. This raises the possibility that all of the 'beneficial' effects relate to negative effects in the placebo group, associated with discontinuation of digoxin. This possibility was explored in several ways.

If there were a withdrawal effect, it was hypothesized that the survival curve for mortality plus CHF hospitalization would be characterized by a single exponential in the digoxin group, but more than one exponential in the placebo group, and that the time constant in the digoxin group would be the same as one of the time constants in the placebo group. Figure 4 below shows the reviewers' analyses of survival (which differ in minor respects from that of the investigators), along with curves representing 1- and 2-exponential decay terms as fit using a non-linear least-squares fitting routine[5]. Neither curve was well fit using a single exponential and both curves were much better fit using 2 exponential decay terms. The fitted values from the double-exponential model are shown in Table 6 below. For both exponential components, the time constant fitted for digoxin is larger than the time constant fitted for placebo.

[4] DIG investigators' analysis.
[5] Splus nls() procedure.

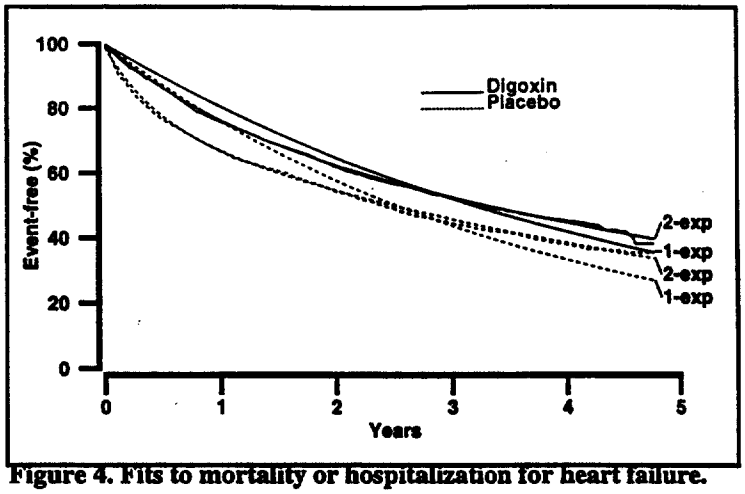

Figure 4. Fits to mortality or hospitalization for heart failure.

Table 6. Fit parameters for mortality or CHF hospitalization.

Fit to $Ae^{-t/\tau_1}+(1-A)e^{-t/\tau_2}$		
	Placebo Fit±SE	Digoxin Fit±SE
A	0.779±0.003	0.835±0.007
τ_1	2041±17	2330±34
τ_2	129±4	286±15

To further explore the possibility of a digoxin withdrawal effect, it would have been useful to compare results among subjects who were on digoxin at randomization to the results for subjects who were naive to digoxin. However, the available historical data only indicate whether subjects had received digoxin in the week prior to randomization. The reviewers performed survival analyses for the combined end point of mortality or hospitalizations for heart failure, separately for subjects who were on digoxin at the time of randomization (about 45% in both treatment groups) vs. subjects who had not been on digoxin in the week before randomization. These survival curves are shown in Figure 5 below. The results demonstrate that prior use of digoxin was a prognostic factor for the end point, but they do not suggest an interaction with randomized treatment[6].

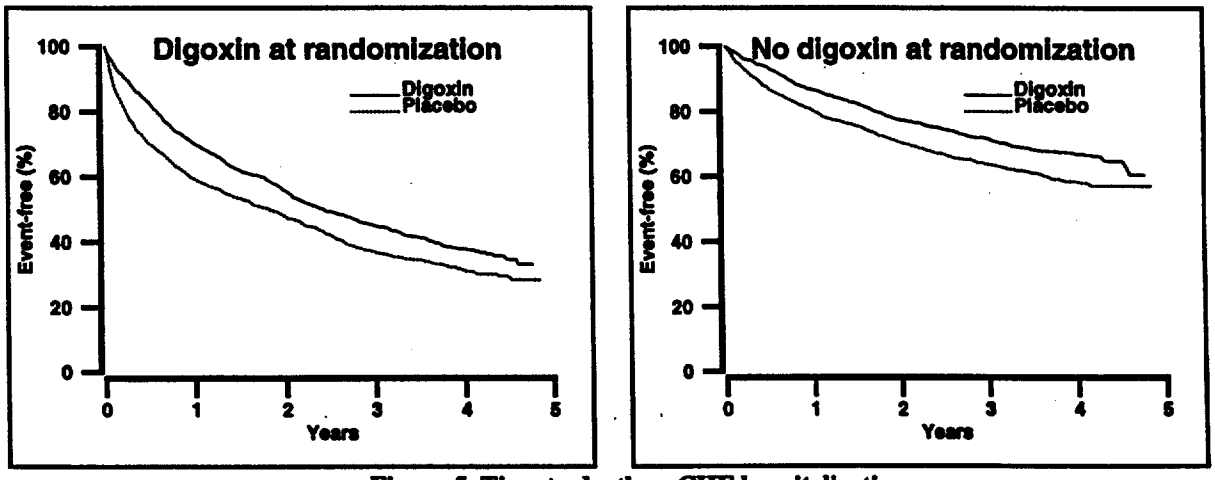

Figure 5. Time to death or CHF hospitalization.

[6] P<0.0001 for comparison of treatment groups in both cases.

Time to first event analysis of all-cause mortality or all-cause hospitalization were analyzed only by the reviewers. Survival curves for mortality or all-cause hospitalization are shown in Figure 6 below, for subjects with EF≤0.45 and EF>0.45. In neither population was there a nominally statistically significant treatment effect, but the difference between treatment groups approaches nominal statistical significance for EF≤0.45[7].

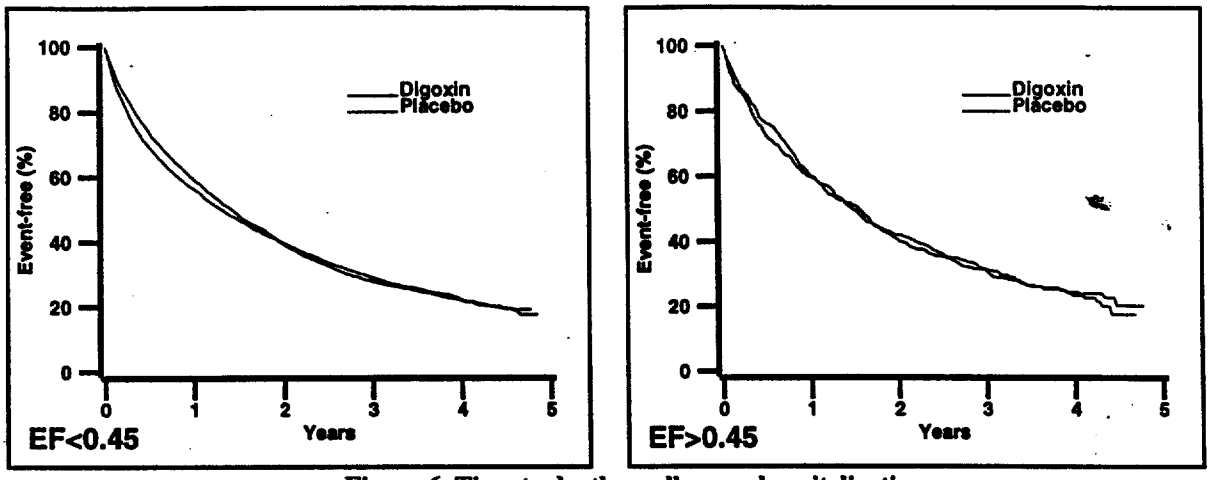

Figure 6. Time to death or all-cause hospitalization.

The proportion of subjects requiring increased medication for heart failure as a function of time in trial is shown in Figure 7 below. There is at least a trend for increased requirements in the placebo group when EF≤0.45.

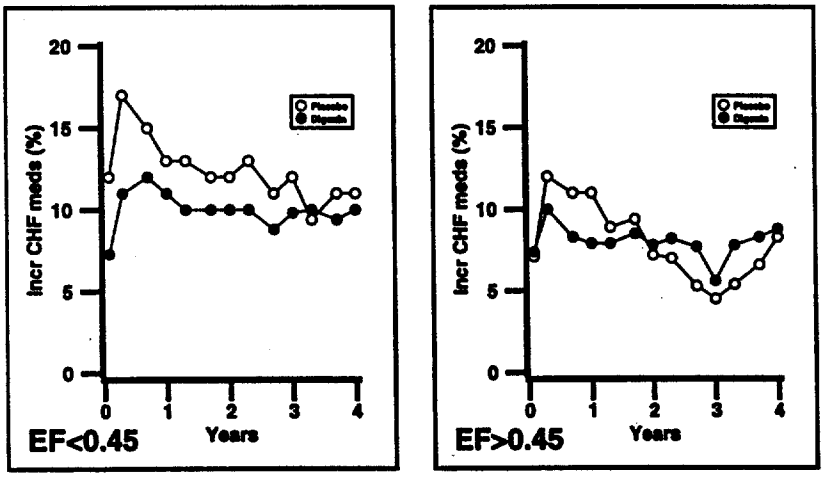

Figure 7. Need for increased CHF medication by study and treatment group.

The proportion of subjects in each NYHA class as a function of time was compared between treatment groups in the study with EF≤0.45, as shown in Figure 8 below. No treatment-related difference is evident.

Suspected digoxin toxicity was reported for 8% of subjects on placebo and 12% of subjects on digoxin when EF≤0.45. Suspected digoxin toxicity was a contributing factor for only about 2% of the 13,000 hospitalizations.

4. Summary and recommendations

How do the results of the DIG trial fit in the context of the earlier RADIANCE and PROVED studies? Both were relatively small (N=178 for RADIANCE, N=88 for PROVED) 12-week, placebo-controlled, digoxin-withdrawal studies in a population with NYHA class II to III heart failure. Subjects in RADIANCE began on digoxin, diuretics, and ACE inhibitor. Subjects in PROVED were on digoxin and diuretics at baseline; ACE inhibitor usage was an exclusion

[7] P=0.074 for EF≤0.45; P=0.86 for EF>0.45.

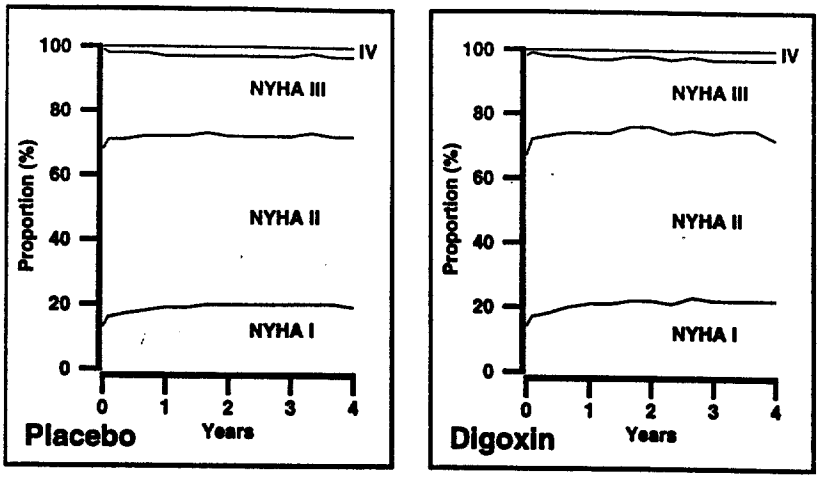

Figure 8. NYHA class by time and treatment group (EF≤0.45).

criterion. Both studies had the same primary end point, change in symptom-limited exercise tolerance, and the same set of secondary end points. Results, all of which were in the direction indicating a treatment benefit where statistically significant, are summarized in Table 7 below. In general, results in the smaller PROVED study trended in favor of a treatment benefit.

Table 7. Results of RADIANCE and PROVED studies.

	RADIANCE N=178	PROVED N=88		RADIANCE N=178	PROVED N=88
ΔETT	*[a]	*	ΔCHF score		
Δ6-min walk	*		ΔNYHA class	*	
Treatment failure[b]	*	*	Subjects' global evaluation	*	
ΔLVEF	*	*	Quality of life	*	
ΔLVEDV	*				

a. P<0.05

b. Either total at 12 weeks or time to event.

The DIG study population included a reasonable fraction of females, non-Caucasians, and elderly subjects. The heart failure was mostly NYHA class I to III, and mostly of ischemic origin.

The main study was among subjects with a baseline EF≤0.45 (N=6801), the primary end point for which was all-cause mortality. Subjects with EF>0.45 were enrolled in a parallel study and followed the same protocol, but no primary end point was declared for this population.

No problems were identified in the conduct of the trial. The study groups were well matched at baseline. More than 70% of subjects remained on study drug at 4 years of follow-up.

All-cause mortality did not differ significantly among subjects randomized to placebo or to digoxin, either in the population with baseline EF≤0.45 or EF>0.45.

There were 6 pre-specified secondary end points. The statistical analysis plan did not allocate α to any of these secondary end points. Among them, nominally statistically significant treatment differences were observed for CHF hospitalizations (28% risk reduction) and all-cause mortality plus CHF hospitalization (15% risk reduction), but not for cardiovascular mortality or non-cardiovascular hospitalization. CHF mortality was associated with a 12% risk reduction with p=0.06. Quality of life data and analyses were not reported.

The DIG investigators in their publication and the sponsor in its submission describe a variety of other non-pre-specified analyses of cause-specific mortality or cause-specific hospitalization, alone and in combination. These analyses were neither reviewed nor reproduced.

The interpretation of this study raises the recurrent regulatory problem of requiring one to decide how much weight to assign an apparent finding among numerous pre-specified secondary end points in a trial which put all of the statistical power in the primary end point and, perhaps relevantly, failed to distinguish a treatment effect.

In this case, the apparent finding is a reduction in hospitalizations for worsening heart failure. For subjects with baseline EF≤0.45, the apparent treatment effect is substantial (15 to 30%) and nominally highly statistically significant, whether one counts subjects with events, counts total events, or analyzes time to all-cause death or first CHF hospitalization. Among pre-specified primary or secondary end points, additional support that this is a real effect of treatment on disease progression can be found in apparent treatment effects on mortality attributed to heart failure (12% risk reduction; p=0.06), but not cardiovascular mortality, not non-cardiovascular hospitalization, not quality of life, and not all-cause mortality. Little additional support can be found among these end points among the (much fewer) subjects with baseline EF>0.45, but time to death or CHF hospitalization shows a similar magnitude of treatment effect (12% risk reduction; p>0.05).

In the RADIANCE and PROVED studies, the effects of digoxin withdrawal on exercise tolerance increased over the 12 weeks of study, although this may have been at least partly attributable to assignment of worst rank to subjects withdrawn from randomized treatment. The DIG study, which was less of a digoxin-withdrawal study than were RADIANCE or PROVED (only about 45% of DIG subjects were on digoxin within 7 days prior to randomization) also demonstrates a long time course for the development of its mostly likely treatment effect—survival curves for mortality plus CHF hospitalization[8] diverge over the first 4 months and maintain a constant separation thereafter.

Recognizing the early and apparently non-progressive nature of effects on CHF hospitalization, the reviewers explored whether this might be attributable to withdrawal of digoxin from the placebo group. Comparison of survival curves for this end point, in a population with EF≤0.45, sub-grouped by use of digoxin at baseline suggests that most of the treatment effect is not restricted to subjects on digoxin at baseline. Furthermore, characterization of the survival curves for mortality plus hospitalization for worsening heart failure requires two exponential terms for the placebo group and two exponential terms, with larger time constants, in the digoxin group. These findings all support a real treatment effect, not an effect attributable to digoxin withdrawal in the placebo group.

The apparent finding of a treatment effect on mortality plus CHF hospitalization in the DIG study is the most compelling evidence of a clinical benefit attributable to use of digoxin—rather than negative effects attributable to its discontinuation—available from any of the RADIANCE, PROVED, and DIG studies.

However, little of the risk reduction in cause-specific hospitalization manifested itself in all-cause hospitalization. The risk reduction is 4 to 6% (depending upon whether one counts all hospitalizations, all hospitalizations not fatal the same day, or subjects with at least one hospitalization), despite the contribution of worsening heart failure to 41% of all hospitalizations. The reviewers conducted a retrospective analysis of time to first event of all-cause mortality or all-cause hospitalization. Differences between treatment groups were not even nominally statistically significant.

There was no evidence of clinical benefit among other data in the DIG study as analyzed by the reviewers. The reviewers conducted exploratory analyses of the need for other heart failure medication and the proportion of subjects in each NYHA class, both as a function of time in study. Almost twice as many placebo subjects with EF≤0.45 required increased heart failure medication early in the study, but the difference between treatment groups declined later in the study. No systematic difference was observed at all among subjects with EF>0.45. There was no difference between treatment groups with respect to the proportion in each NYHA class at any point in the study.

The only claim clearly supportable from the DIG study is, therefore, the lack of effect on mortality (with expressed confidence limits), making it the only inotropic agent so distinguished. What, if anything, the label should say about hospitalization is certain to be more controversial. The reviewers find the evidence fairly compelling that there is a beneficial treatment effect on hospitalizations for heart failure, but they would argue that there is a lack of net benefit, when one considers all-cause hospitalization.

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[8] Figure 3 on page 8.

5. Label review

On the pages that follow, the sponsor's submitted proposed label appears in the left column. In the right column, where applicable, the reviewers have placed comments or revised text. In areas where there are no reviewer comments, the text conforms to the intent expressed in the marked-up label sent to the firm with the "approvable" letter of 14 February 1996.

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17 pages

PURGED

(DRAFT LABELING)

Steven M. Rodin, M.D.
Medical Officer

Food and Drug Administration

Division of Cardio-Renal Drugs
Tel 301-443-0320; FAX-9283

Medical Review of NDA

JAN 24 1994
JAN 25 1994

1 General information

NDA #:	**20-405**
Drug:	**Digoxin** (Lanoxin®)
Sponsor:	Burroughs Wellcome Company
Proposed indication:	oral treatment of congestive heart failure (CHF) in patients receiving diuretics with or without angiotensin converting enzyme inhibitors
related NDAs:	9-330 (parenteral formulation) 18-118 (Lanoxicaps®)
related INDs:	
Pharmacologic type:	digitalis glycoside
Date of NDA submission:	30 September 1993
Reviewer:	Steven M. Rodin, M.D.
Review last revised:	24 January 1994

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2 **Table of contents**

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3 Background

Digoxin (Lanoxin®, Burroughs Wellcome Company) is approved for congestive heart failure (CHF), however it has been marketed since prior to the 1962 Kefauver-Harris Amendment, and there is no approved NDA for the tablet formulation (although an approved NDA (18-118) exists for the encapsulated formulation (Lanoxicaps®, Burroughs Wellcome Company)). The sponsor had been requested by FDA to submit an NDA for the tablet with support to be drawn from the published literature. They have instead submitted the results of 2 placebo-controlled withdrawal studies of CHF patients taking angiotensin converting enzyme (ACE) inhibitors and/or diuretics ("RADIANCE" and "PROVED" trials), in addition to publications from placebo-controlled studies. The sponsor proposes to market a new tablet formulation[1], and requests 3 years of marketing exclusivity for the indication, "... for the treatment of heart failure in patients receiving ACE inhibitors and diuretics, or diuretics alone."

The currently approved heart failure indication for Lanoxin® tablets reads: "The increased cardiac output resulting from the inotropic action of digoxin ameliorates the disturbances characteristic of heart failure (venous congestion, edema, dyspnea, orthopnea and cardiac asthma). Digoxin is more effective in "low output" (pump) failure than in "high output" heart failure secondary to arteriovenous fistula, anemia, infection or hyperthyroidism. Digoxin is usually continued after failure is controlled, unless some known precipitating factor is corrected. Studies have shown, however, that even though hemodynamic effects can be demonstrated in almost all patients, corresponding improvement in the signs and symptoms of heart failure is not necessarily apparent. Therefore, in patients in whom digoxin may be difficult to regulate, or in whom the risk of toxicity may be great (e.g., patients with unstable renal function or whose potassium levels tend to fluctuate) a cautious withdrawal of digoxin may be considered. If digoxin is discontinued, the patient should be regularly monitored for clinical evidence of recurrent heart failure."

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[1]see the biopharmaceutical review of bioequivalence study Q25:01-01. This compared a new 0.5 mg tablet, a new 0.0625 mg tablet, and the currently marketed 0.125 mg tablet (used in the submitted "RADIANCE" and "PROVED" trials).

4 Clinical efficacy trials

4.1 *Trials with submitted databases*:

4.1.1 "RADIANCE" study 437)

SUMMARY:

This placebo-controlled, double-blind, parallel-group withdrawal study randomized 178 subjects (NYHA class II-III CHF patients in NSR who were previously treated with a diuretic, an ACE inhibitor, and digoxin) to 12 weeks of placebo or digoxin therapy (in addition to background diuretic and ACE inhibitor therapy). The principal objectives were to evaluate mean changes from pre-withdrawal duration of symptom-limited exercise, and six minute walk distance, as well as the comparative rates of treatment failure during the withdrawal period.

PROTOCOL:

▸ **Enrollment criteria:**

Enrolled subjects were NYHA class II-III CHF patients in NSR who were previously treated with a diuretic, an ACE inhibitor, and digoxin for at least 3 months. Excluded were patients manifesting:

- CHF secondary to uncorrected thyroid disease, active myocarditis, or known amyloid cardiomyopathy.
- myocardial infarction (MI) within the previous 3 months, severe or unstable angina, valvulopathy, hypertrophic cardiomyopathy, symptomatic ventricular arrhythmias, hypertension, atrial fibrillation, or paroxysmal supraventricular tachycardia.
- functional evidence of chronic obstructive lung disease.
- serum potassium concentration < 3.5 or > 5.3 mEq/L.
- cerebrovascular accident within the past year.
- serum creatinine concentration > 2.5 mg/dL.
- a requirement for cardioactive drugs (other than diuretics, ACE inhibitors, sublingual nitroglycerin, or stable doses of long-acting nitrates).

▸ **Qualifying criteria:**

In order to qualify patients had to manifest stable CHF during a single-blind, 8 week run-in period during which optimum fixed doses of digoxin (achieving serum concentrations of 0.9-2.0 ng/mL), diuretic, and ACE inhibitor were established. The duration of symptom-limited treadmill exercise (modified Naughton protocol) had to be 2-14 minutes, and reproducible within 1 minute.

▸ **Treatment regimen:**

Qualified patients were randomly assigned either to continued digoxin or to placebo (in addition to background diuretic and ACE inhibitor therapy) during a 12 week double-blind withdrawal period. The minimum enalapril dose was to have been 5 mg/d (once or twice daily), and the minimum captopril dose was 25 mg/d (divided into two or three daily doses).

▸ **Endpoints:**

The primary objectives were to evaluate the mean changes from pre-withdrawal duration of symptom-limited exercise, pre-withdrawal distance of a six minute walk, and the proportion of treatment failures in each group. Treatment failure was defined as death or a worsening of CHF symptoms requiring an increase in the pre-randomization diuretic and/or ACE inhibitor dose, the addition of other medications, or a requirement for treatment of CHF symptoms in an emergency room (ER) or hospital.

Symptom[2]-limited treadmill exercise tests (modified Naughton protocol) were performed at the digoxin interdosing interval at the end of post-withdrawal weeks 2, 6, and 12. The total distance of a dyspnea or fatigue-limited 6 minute walk was also assessed at the digoxin interdosing interval at the end of post-withdrawal weeks 4, 8, and 10.

A CHF score was used to measure the severity of dyspnea, rales, standing tachycardia, right heart failure, jugular venous distention (JVD), and chest radiographic abnormality (the overall score could range from 0 (least severe abnormality) to 13 (most severe)). Changes in NYHA class were assessed, and the patients also provided a Global Evaluation of Progress[3]

Quality of life (the patients' perceptions of the physical, socioeconomic, and psychological impact of CHF) was assessed via the Minnesota Living With Heart Failure Questionnaire (responses were scored over the range of 0 (no impact of life quality) to 5 (very much impact)).

Left ventricular end-diastolic (LVED) diameter was measured by M-mode echocardiography at the start of withdrawal and at post-withdrawal week 12.

[2]dyspnea or fatigue.

[3]progress was evaluated as unchanged, or much, moderately, or slightly changed (better vs worse).

▸ **Statistical procedures:**

• **Dataset analyzed:**

Two hundred sixteen patients entered the run-in. Eighteen percent discontinued during the run-in (for adverse experiences (AE), protocol violations, and failure to meet the entry criteria). The study randomized 178 patients (93 to placebo, and 85 to digoxin). Thirty seven percent of the placebo-randomized patients discontinued during the withdrawal period (because of treatment failure, AE, protocol violations, loss to follow-up, nonconsent, and diuretic noncompliance). Fourteen percent of the digoxin-randomized patients discontinued during the withdrawal period (because of treatment failure, loss to follow-up, and diuretic noncompliance). Excluded from efficacy analyses were all exercise tests in which the patient failed to perceive an appreciable exertion (i.e. perceived exertion scored at a level ≥19 on the Borg Scale).

• **Handling of missing data:**

A lowest rank was assigned (and carried foward) for treadmill exercise duration, walk distance, NYHA Class, and Global Evaluation of Progress when data were missing because of treatment failure. Where treadmill exercise data, walk distance data, or CHF score were missing for reasons other than treatment failure, the last nonmissing values were carried forward.

• **Analyses performed:**

The prespecified analysis was a chi-square test of the proportion of treatment failures. A survival analysis of the time-to-treatment failure was also performed, and cumulative treatment failure probabilities were assessed with the Logrank test. A Cochran-Mantel-Haenszel (CMH) test was used to compare treatment groups at each time point during the withdrawal period, and changes from pre-withdrawal CHF score were analyzed using the mean rank score version of the CMH statistic.

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RESULTS:

▸ **Treatment group comparability:**

• **Demographics:**

Mean age and body weight as well as the distribution of race, and sex were comparable in the two groups at the start of the withdrawal.

• **Disease severity:**

With respect to treadmill exercise duration, the placebo group tended to have less severe CHF than did the digoxin group[4] (at the start of the withdrawal), although with respect to the proportion of patients with pulmonary rales the placebo group appeared to have more severe CHF[5]. All other indices (median walk distance, NYHA class, radionuclide left ventricular ejection fraction (LVEF), LVED diameter, CHF score, and quality of life score) were comparable (or not statistically significantly different) in the 2 treatment groups at the start of the withdrawal.

• **Exposure to randomized therapy:**

The mean digoxin doses were comparable in the 2 treatment groups at the start of the withdrawal.

• **Exposure to ACE inhibitor therapy:**

The mean pre-withdrawal dose of ACE inhibitors in the 2 treatment groups remains to be characterized.

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[4]the median exercise duration was 571 vs 510 seconds in the placebo vs digoxin groups, respectively (p = 0.09).

[5]12 vs 7% had rales in the placebo vs digoxin groups, respectively (p = 0.01).

▸ **Efficacy outcomes:**

Duration of symptom-limited exercise:

When the lowest rank was assigned to treatment failures (and carried foward), the discontinuation of digoxin therapy was associated with a 27 second deterioration in median exercise duration after 12 weeks, whereas the median exercise duration increased by 18.5 seconds in patients who received continuous digoxin treatment. The difference in the adjusted mean change from pre-withdrawal duration of symptom-limited treadmill exercise was statistically significant at post-withdrawal week 12 ($p = 0.05$), but not at post-withdrawal weeks 2 or 6.

Table 1:

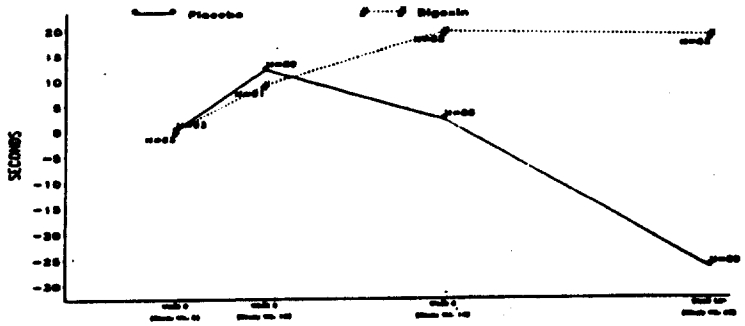
Adjusted median change from pre-withdrawal duration of symptom-limited treadmill exercise [lowest rank assigned to treatment failures; study 437]:

Post-withdrawal week	*Median change (sec):*		*p value*
	Placebo	**Digoxin**	
2	12.0	9.0	0.96
6	2.0	19.5	0.42
12	-27.0	18.5	0.05

[source: modification of table 3-2, page 253, vol 1.9]

Figure 1:

Graphical depiction of the data in the above table



[source: modified photocopy of figure 1-2, page 517, volume 1.9]

At week zero (the start of the withdrawal period), group medians were 571 vs 510 seconds in the placebo vs digoxin groups, respectively. The CMH analysis assigned and carried foward a lowest rank when data were missing because of treatment failure. Measurements were obtained at the digoxin interdosing interval.

▸ **Efficacy outcomes** [continued]:

Distance of the 6 minute walk:

When the lowest rank was assigned to treatment failures (and carried foward), the between-group differences in the adjusted median change from pre-withdrawal walk distance were statistically significant at each observation point (post-withdrawal weeks 4, 8, and 10). The greatest treatment difference in median change in walk distance was seen at post-withdrawal week ten (125 feet; p = 0.02).

Table 2:

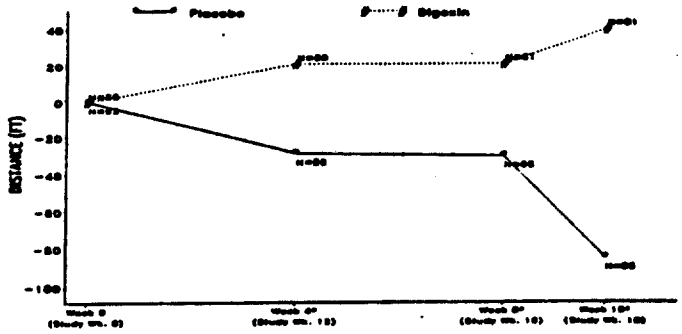
Adjusted median change from pre-withdrawal distance of the 6 minute walk [lowest rank assigned to treatment failures; study 437]:

Post-withdrawal week	*Median change (feet):*		*p value*
	Placebo	**Digoxin**	
4	-28.5	21.0	0.002
8	-30.0	21.0	0.045
10	-85.0	40.0	0.021

[source: modification of table 5-2, page 143 , vol 1.9]

Figure 2:

Graphical depiction of the data in the above table



[source: modifiied photocopy of figure 2-2, page 519, volume 1.9]

At week zero (the start of the withdrawal period), group medians were 1215 vs 1140 feet in the placebo vs digoxin groups, respectively. The CMH analysis assigned a lowest rank when data were missing because of treatment failure. Measurements were obtained at the digoxin interdosing interval.

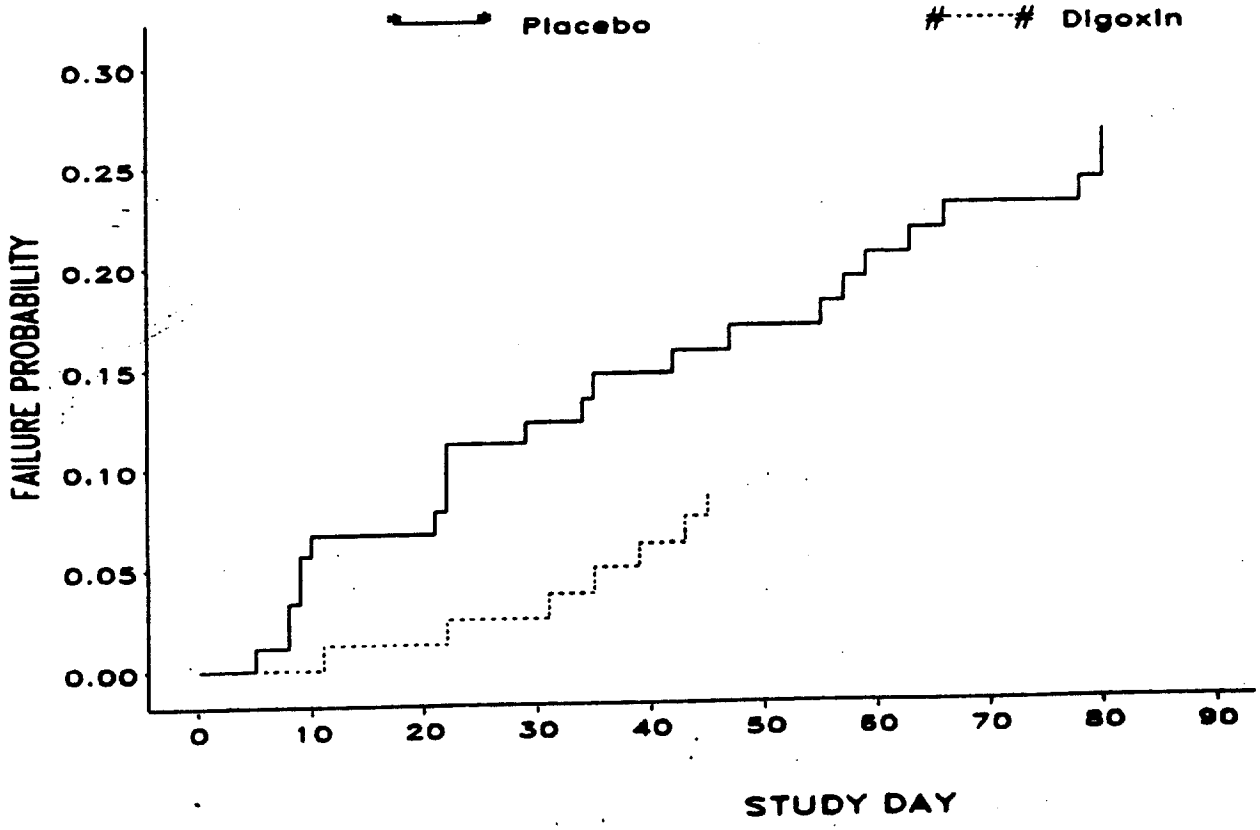
▸ **Efficacy outcomes** [continued]:

Treatment failures:

There was a statistically significant difference in the proportion of treatment failures, these occurred in 8% of the digoxin group vs 25% of the placebo group (p=0.003, Pearson Chi-square statistic). The median time to treatment failure in the 2 treatment groups remains to be characterized, however the sponsor did report that it was significantly shorter in the placebo group (p=0.003, log rank test). The breakdown of treatment failures into deaths, increases in drug therapy, ER admissions, and hospitalizations also remains to be characterized.

Figure 3:

Kaplan-Meir estimate of the cumulative probability of treatment failure following digoxin withdrawal (study 437):



[source: modified photocopy of figure 3, page 520, volume 1.9]

▸ **Efficacy outcomes** [continued]:

LVEF:

A significantly larger adjusted mean decrease from pre-withdrawal LVEF was observed in the placebo group (-4.1 percentage points) than in the digoxin group (-0.5 percentage points; p = 0.001).

LVED diameter:

The placebo group manifested an adjusted mean *increase* from pre-withdrawal LVED diameter (+0.8 mm) whereas the digoxin group had an adjusted mean *decrease* from pre-withdrawal LVED diameter (-1.4 mm; p= 0.04).

Signs and symptoms of CHF:

A larger proportion of digoxin-treated patients experienced an improvement over the pre-withdrawal level of fatigue (24%) than did placebo patients (12%; p = 0.04). No other sign or symptom of CHF was statistically distinguishable in the 2 groups (although there was a trend (p = 0.08) towards a lesser proportion of digoxin-treated patients (6%) manifesting a worsening of JVD, relative to placebo patients (15%).

[CONTINUED NEXT PAGE]

▸ **Efficacy outcomes** [continued]:

CHF score:

No statistically significant treatment difference was observed with respect to the change from pre-withdrawal CHF score at week 12 post-withdrawal (p=0.26). See the table below.

NYHA class:

There was a significant treatment difference, with respect to the change from pre-withdrawal NYHA Class at week 12 post-withdrawal (p = 0.02). By this time a larger proportion of placebo patients had manifested moderate worsening in NYHA Class than had digoxin-treated patients (21 vs 7%, respectively). See the table below.

Patients' Global Evaluation of Progress:

With respect to the Patients' Global Evaluation of Progress at week 12 post-withdrawal, a significant treatment difference was observed. A larger proportion of placebo patients manifested moderate worsening than did digoxin-treated patients (13 vs 4%, respectively), and a lesser proportion of placebo patients manifested moderate improvement than did those administered digoxin (9 vs 14%, respectively; p = 0.007). See the table below.

Quality of Life:

A significant treatment difference was observed with respect to the change from pre-withdrawal score for the Overall Quality of Life at week 12 post-withdrawal (p = 0.04). A larger proportion of digoxin patients manifested improvement than did placebo-treated patients (47 vs 33%, respectively). See the table below.

Table 3:

Change from pre-withdrawal status of various metrics at post-withdrawal week 12 (study 437)

	CHF score		*NYHA class*		*Global progress*		*Overall quality of life*	
	placebo	dig	placebo	dig	placebo	dig	placebo	dig
% who improved	4	0	3	6	9	14	33	47
% without change	45	51	69	84	32	29	18	12
% who worsened	5	4	21	7	13	4	46	41
Significance of treatment effect	p=0.26		p=0.02		p=0.007		p=0.04	

[source: modification of tables 7-20, 7-21, 8-2, & 9-2; pages 233, 241, 245, & 249; vol 1.9]

RADIANCE study (GBHA 437)

COMMENTS (study 437)

1. In the RADIANCE trial the discontinuation of oral digoxin in NYHA class II-III CHF patients in NSR who were stabilized on ACE inhibitors and/or diuretics resulted in a significant deterioration in the median duration of symptom-limited exercise ($p = 0.05$, relative to the continuously digoxin-treated group), and a significantly increased occurrence of death or a requirement for treatment intervention for CHF ($p = 0.003$).

As with any withdrawal design, it can be argued that the apparent evidence of drug effect (as inferred by post-withdrawal differences in the withdrawn vs continuously treated groups) may be artefactual, i.e. arising as a result of nothing more than rebound worsening upon drug withdrawal, without any benefit actually attributable to drug. Nonetheless, within the limits of withdrawal design the results of the RADIANCE trial support the inference that digoxin improves exercise duration in CHF and reduces deaths or worsening CHF.

2. When data were missing on the basis of treatment failure a lowest rank was assigned for functional endpoints (treadmill exercise duration, walk distance, NYHA Class, and Global Evaluation of Progress), and treatment failure was a combined endpoint which pooled deaths and cases of symptomatic deterioration. If a drug were superior to placebo with respect to survival benefit this method could bias the results towards overestimating drug effect on nonfatal morbidity endpoints (since a relatively greater proportion of placebo patients would die, and then have worst ranks assigned for morbidity endpoints). A precise estimate of the population survival effect of digoxin is presently unavailable, but in this trial the evidence supports the view that a bias of this sort would not have been operative since there was no greater crude proportion of deaths in the placebo-randomized vs digoxin-randomized groups (2.2 vs 4.7%, respectively). Indeed in a published analysis which excluded deaths from the definition of treatment failures, the reported treadmill exercise results were comparable to those reported in this NDA [New England Journal of Medicine 1993;329:1-7].

3. The intention of the pre-randomization run-in was to produce 2 groups of optimally treated patients. Reasonable skeptics may raise the question of whether the ultimately placebo-randomized group was, at the start of the withdrawal, less optimally treated than the ultimately digoxin-randomized group[6]. Such a concern would be supported by the finding that a significantly greater proportion of placebo patients had pulmonary rales at this time, but should be mitigated by the fact that mean, pre-withdrawal exercise duration tended to be longer in the placebo group.

[6]a description of comparative mean ACE inhibitor doses is pending.

4.1.2. "PROVED" study (436):

SUMMARY:

This placebo-controlled, double-blind, parallel-group withdrawal study randomized 88 subjects (NYHA Class II-III CHF patients in NSR) to 12 weeks of placebo, or digoxin therapy (in addition to background diuretic therapy). The primary objectives of this study were to evaluate the change from pre-withdrawal duration of symptom-limited exercise, and six minute walk distance, as well as the comparative rates of treatment failure.

PROTOCOL:

▸ **Enrollment criteria:**

Enrolled subjects were NYHA class II-III patients in NSR for whom chronic CHF was not precipitated by acute myocardial ischemia. Enrollees had a resting LVEF ≤ 35%, echocardiographic LVED diameter of 34-60 mm/m^2, and a symptom-limited exercise duration of 2-12 minutes during a modified Naughton protocol. All were previously treated with a diuretic, and digoxin.

The exclusion criteria did not appreciably differ from those described above for study 437.

▸ **Qualifying criteria:**

In order to qualify patients had to manifest stable CHF during a single-blind, 8 week run-in period during which optimum fixed oral doses of digoxin (once-daily administrations achieving serum concentrations of 0.9-2.0 ng/mL), and diuretic were established. In addition, the duration of CHF symptom-limited treadmill exercise (using a modified Naughton protocol) had to be 2-14 minutes, and reproducible within 1 minute.

▸ **Treatment regimen:**

Qualified patients were randomized to either continued digoxin (at the final dose administered during the run-in), or to placebo (in addition to a background diuretic at the final dose established during the run-in). The double-blind withdrawal period was 12 weeks in duration.

PROVED study 436)

▸ **Endpoints:**

The primary objectives, endpoint definitions, and measurement methodology were identical to those described under study 437. These are repeated below, for convenience.

The primary objectives were to evaluate the mean change from pre-withdrawal duration of symptom-limited exercise at "endpoint" (the final observation during the withdrawal), the mean change from pre-withdrawal 6 minute walk distance, and the comparative proportion of "treatment failures" in each group (defined as death, or a worsening of CHF symptoms requiring an increase in drug therapy and/or necessitating treatment in an ER or hospital).

Symptom (dyspnea or fatigue)-limited exercise tests were performed, according to the modified Naughton treadmill protocol, at the digoxin interdosing interval at the end of post-withdrawal weeks 2, 6, and 12. The total distance of a symptom (dyspnea or fatigue)-limited 6 minute walk was assessed at the digoxin interdosing interval at the end of post-withdrawal weeks 4, 8, and 10.

Secondary efficacy endpoints were the time to treatment failure, clinical signs and symptoms of CHF, CHF Score, NYHA class, patients' Global Evaluation of Progress, quality of life score, LVEF, and echocardiographic LVED diameter.

▸ **Statistical procedures:**

• **Dataset analyzed:**

One hundred thirteen patients entered the run-in. The study randomized 88 patients (46 to placebo, and 42 to digoxin). Forty-six percent of the placebo-randomized patients discontinued during the withdrawal period because of either treatment failure, AE, protocol violation, loss to follow-up, or nonconsent. Twenty-four percent of the digoxin-randomized patients discontinued during the withdrawal period because of either treatment failure, AE, or nonconsent. Excluded from efficacy analyses were all exercise tests in which the patient failed to perceive an appreciable exertion (i.e. perceived exertion scored at a level ≥19 on the Borg Scale).

• **Handling of missing data:**

When data were missing because of treatment failure a lowest rank was assigned (and carried foward) for treadmill exercise duration, walk distance, NYHA Class, and Global Evaluation of Progress. The last nonmissing values were carried forward when treadmill exercise data, walk distance data, or CHF scores were missing for reasons other than treatment failure.

• **Analyses performed:**

The prespecified analysis was a chi-square test of the proportion of treatment failures. A survival analysis of the time-to-treatment failure was also performed, and cumulative treatment failure probabilities were assessed with the Logrank test. A CMH test was used to compare treatment groups at each time point during the withdrawal period.

RESULTS:

▸ **Treatment group comparability:**

• **Demographics:**

Mean age as well as the distribution of race and sex were comparable in the two groups at the start of the withdrawal.

• **Disease severity:**

Prior to withdrawal JVD was significantly more prevalent in the digoxin-group than in the placebo group (45 vs 22%, respectively; p=0.02), and a lesser proportion of digoxin patients (33%) than placebo patients (50%) experienced little to no impact of CHF on their quality of life (p=0.04; Physical Dimension component of this metric). The pre-withdrawal median exercise duration tended to be longer in the placebo group (46.5 second difference, p=0.91), and the pre-withdrawal 6 minute walk distance tended to be longer in the digoxin group (66 foot difference, p=0.84).

• **Exposure to randomized therapy:**

Digoxin doses ranged from 0.125 to 0.5 mg/d.

• **Exposure to ACE inhibitor therapy:**

The mean pre-withdrawal dose of ACE inhibitors in the 2 treatment groups was not characterized.

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▸ **Efficacy outcomes:**

Duration of symptom-limited exercise:

When the lowest rank was assigned to treatment failures (and carried foward), the discontinuation of digoxin therapy was associated with a 96 second deterioration in median exercise duration after 12 weeks, whereas the median exercise duration *increased* by 4.5 seconds in patients who received continuous digoxin treatment. The difference in the adjusted mean change from pre-withdrawal duration of symptom-limited treadmill exercise was statistically significant ($p \leq 0.05$) at each post-withdrawal observation (weeks 2, 6, and 12).

Table 4:

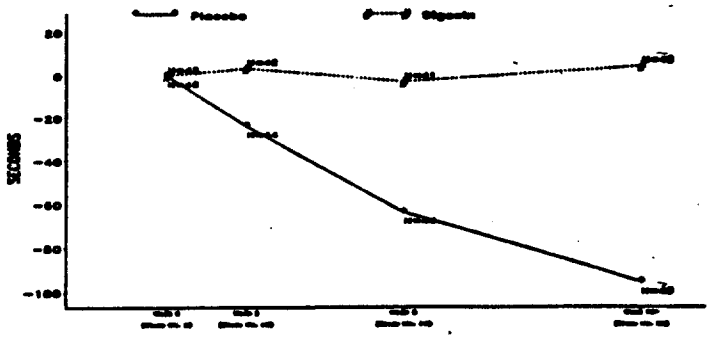
Adjusted median change from pre-withdrawal duration of symptom-limited treadmill exercise [lowest rank assigned to treatment failures; study 436]:

Post-withdrawal week	*Median change (sec):*		*p value*
	Placebo	**Digoxin**	
2	-24.0	3.5	0.05
6	-64.0	-3.0	0.03
12	-96.0	4.5	0.003

[source: modification of table 3-2, page 4255, vol 1.19]

Figure 4:

Graphical depiction of the data in the above table



[source: modified photocopy of figure 1-2, page 4303, volume 1.19]

At week zero (the start of the withdrawal period), group medians were 542 vs 494 seconds in the placebo v digoxin groups, respectively. The CMH analysis assigned and carried foward a lowest rank when data were missing because of treatment failure. Measurements were obtained at the digoxin interdosing interval.

▸ **Efficacy outcomes** [continued]:

Distance of the 6 minute walk:

When the lowest rank was assigned to treatment failures (and carried foward) there were no statistically distinguishable treatment differences in the median change from pre-withdrawal walk distance, although the magnitude of median decreases did tend to be larger in the placebo group at post-withdrawal weeks 8 and 10 (see the table below).

Table 5:

Adjusted median change from pre-withdrawal distance of the 6 minute walk [lowest rank assigned to treatment failures; study 436]:

Post-withdrawal week	*Median change (feet):*		*p value*
	Placebo	**Digoxin**	
4	0.0	-28.0	0.38
8	-105.0	0.0	0.18
10	-42.0	-22.5	0.73

[source: modification of table 5-2, page 4258 , vol 1.19]

▸ **Efficacy outcomes** [continued]:

Treatment failures:

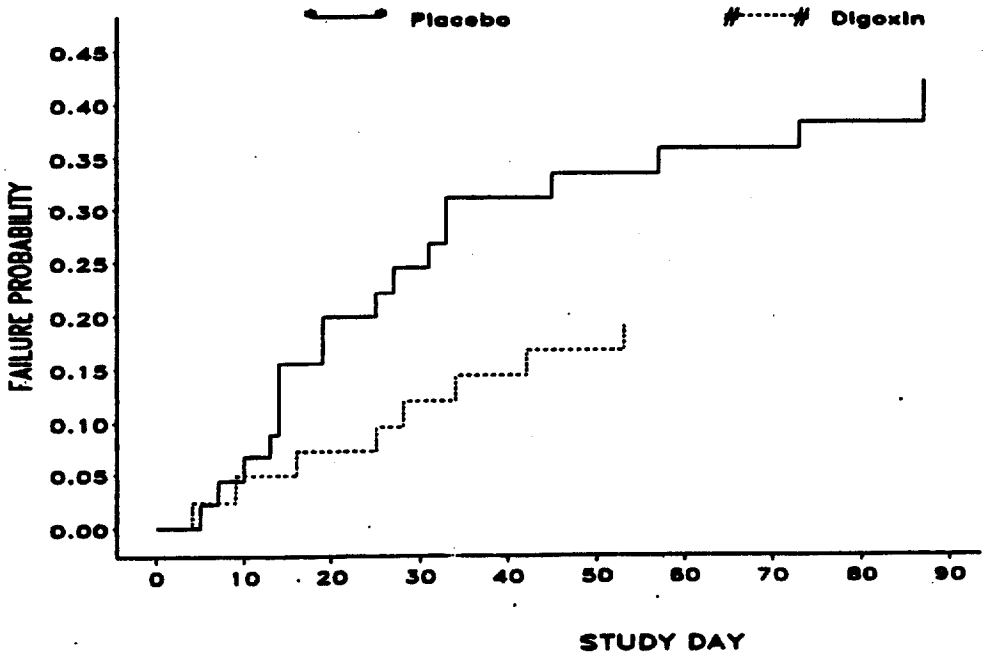
The proportion of treatment failures was significantly greater in the placebo group than in the digoxin group (39 vs 19%, respectively; p=0.04). The median time to treatment failure in the 2 groups is pending, however the sponsor did report that, on average, the placebo group deteriorated in a significantly more rapid fashion (p=0.047).

Of the 18 placebo patients who were blindly classified[7] as having met the protocol definition of treatment failure, 1 died, 10 required an increase in drug therapy, 1 needed treatment in an ER, and 6 were admitted to a hospital for worsening CHF.

Of the 8 digoxin patients who were blindly classified as having met the protocol definition of treatment failure, 1 died, 4 required an increase in drug therapy, none needed treatment in an ER, and 3 were admitted to a hospital for worsening CHF.

Figure 5:

Kaplan-Meir estimate of the cumulative probability of treatment failure following digoxin withdrawal (study 436):



[source: modified photocopy of figure 3, page 4506, volume 1.19]

[7]this blinded review of both treatment groups resulted in the appropriate reclassification of four patients who were incorrectly designated as treatment failures by the investigators.

▸ **Efficacy outcomes** [continued]:

LVEF:

With respect to the change from pre-withdrawal LVEF at endpoint, a statistically significant treatment difference was observed (p = 0.02). The placebo group manifested an adjusted mean change from pre-withdrawal LVEF of -3.4 percentage points, whereas the digoxin group demonstrated a mean change of 1.7 percentage points.

LVED diameter:

The change from pre-withdrawal LVED at endpoint was not statistically distinguishable in the two treatment groups. The placebo group manifested an adjusted mean change from pre-withdrawal LVED diameter of +1.3 mm, whereas the digoxin group demonstrated an adjusted mean change of -0.4 mm (p= 0.34).

Signs and symptoms of CHF:

At week 12 post-withdrawal there was a trend towards a lesser proportion of digoxin-treated patients manifesting a worsening of JVD, relative to placebo-treated patients (8% vs 28%, respectively; nominal p value of 0.09).

CHF score:

No statistically significant treatment difference was observed with respect to the change from pre-withdrawal CHF score at week 12 post-withdrawal (p = 0.12). See the table on the next page.

NYHA class:

The change from NYHA Class at week 12 post-withdrawal was not statistically distinguishable in the two treatment groups (p = 0.32). See the table on the next page.

Patients' Global Evaluation of Progress:

The change from pre-withdrawal Global Evaluation of Progress was not statistically distinguishable in the two treatment groups at week 12 post-withdrawal (p = 0.46). See the table on the next page.

▸ **Efficacy outcomes** [continued]:

Quality of Life:

No statistically significant treatment difference was observed with respect to the change from pre-withdrawal score for the overall quality of life at post-withdrawal week 12 (p = 0.74). See the table below:-

Table 6:

Change from pre-withdrawal status of various metrics at post-withdrawal week 12 (study 436)

	CHF score		*NYHA class*		*Global progress*		*Overall quality of life*	
	placebo	dig	placebo	dig	placebo	dig	placebo	dig
% who improved	0	7	2	10	7	7	35	45
% without change	54	48	61	64	22	33	26	17
% who worsened	0	10	15	14	7	2	39	36
Significance of treatment effect	p=0.12		p=0.32		p=0.46		p=0.74	

[source: modification of tables 7-20, 7-21, 8-2, & 9-2; pages 218, 226, 230, & 234; vol 1.19]

COMMENTS (study 436):

1. Within the limits of withdrawal design the results of the PROVED trial support the inference that digoxin improved exercise duration in CHF and reduced the proportion of patients manifesting worsening CHF. In this trial the discontinuation of oral digoxin in NYHA class II-III CHF patients in NSR who were stabilized on diuretics resulted in a clinical deterioration in the median duration of symptom-limited exercise[8] (by 100.5 sec; p = 0.003), and an increased requirements for treatment interventions for CHF (20 percentage point difference in the proportion of treatment failures; p = 0.04).

2. A bias towards overestimating digoxin's effect on morbidity endpoints (potentially arising from the assignment of lowest rank to treatment failures (see comments for study 437)) would not plausibly have been operative since there was no greater crude proportion of deaths in the placebo vs digoxin-randomized groups (2.2 vs 2.4%, respectively).

[8]unlike the RADIANCE trial, the effect on exercise duration was discernible within 2 weeks of digoxin withdrawal.

4.2 Previously published studies:

4.2.1 Publication of The Captopril-Digoxin Multicenter Research Group

CITATION: Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure: The Captopril-Digoxin Multicenter Research Group. JAMA 1988; 259: 539-544.

SUMMARY:

This placebo-controlled, double-blind, parallel-group study randomized 196 subjects[9] (NYHA class II-III CHF patients in NSR) to receive digoxin, or placebo for 24 weeks. The objectives included an assessment of the mean change from the pre-study duration of symptom-limited exercise, and the comparative proportions requiring hospitalization, ER visits for CHF, or additional diuretic therapy.

PROTOCOL:

▸ **Enrollment criteria:**

Enrolled subjects were NYHA class II-III CHF patients younger than 75 years who manifested a LVEF ≤ 40%, and whose duration of symptom-limited treadmill exercise was greater than 4 minutes but less than the predicted maximum. Excluded from enrollment were patients manifesting:

- a requirement for concomitant inotropic agents, vasodilators, β-adrenoreceptor antagonists, or calcium antagonists.
- myocardial infarction within the preceding two months, unstable angina, hypertension despite diuretic therapy, or pulmonary disease.

▸ **Qualifying criteria:**

During a run-in period of at least 10 days duration any previous digitalis glycosides, vasodilators, and/or nonglycoside positive inotropic agents were discontinued, and any diuretics were dose-stabilized. Patients qualified for randomization if they tolerated withdrawal of these medications, reproducibly exercised for greater than 4 minutes (with a modified Naughton protocol), and tolerated a single 25 mg oral captopril dose.

[9]not including the captopril arm.

▸ **Treatment regimen:**

Qualified patients were randomized to once daily oral doses of digoxin (0.125-0.375 mg/d; titrated to achieve trough serum levels of 0.9-3.2 nmol/L (0.7- 2.5 ng/mL)), or placebo for 24 weeks. Random changes in placebo dose were made to maintain the blind.

▸ **Endpoints:**

The principle endpoints were the mean change from the pretreatment duration of symptom (dyspnea or fatigue[10])-limited treadmill exercise. The time at which exercise tests were performed, relative to digoxin dosing, was not described. Mean changes from pre-withdrawal functional class, and pre-withdrawal LVEF were examined, as was the proportion of patients requiring additional diuretic treatment (at the *end* of the double-blind, as opposed to at any time in the study), the proportion requiring hospitalization or ER visits for CHF, and the proportion whose CHF progressed despite additional diuretic therapy ("treatment failures"[11]).

▸ **Statistical procedures:**

• **Dataset analyzed:**

Thirty patients were withdrawn during the run-in because of worsening CHF following discontinuation of their nondiuretic CHF medications. The reported dataset excluded patients who deviated from randomized therapy (with the exception of the intent-to-treat analysis of LVEF data).

• **Handling of missing data:**

It is not clear how missing data were handled.

• **Analyses performed:**

Analysis of covariance (ANCOVA) was used to adjust for pre-withdrawal levels of exercise duration, and LVEF. Differences in functional class were compared among treatment groups using a Mantel-Haenszel test. A two-tailed Fisher's exact test was used for the metrics which involved proportions.

[10]the specific symptom limitations were garnered from the Medical Officer's review of captopril NDA 18-3453/S40.

[11]the definition of treatment failure derives from the Medical Officer's review of captopril NDA 18-3453/S40.

RESULTS:

▸ **Treatment group comparability:**

• **Demographics:**

Among digoxin-randomized patients a lesser proportion used digoxin prior to the study (69%), compared to placebo-randomized patients (87%). There was a balanced distribution of pre-study diuretic use among these two treatment groups (86-88% of patients had previously used diuretics).

• **Disease severity:**

A greater mean, pre-treatment exercise duration was manifest among digoxin-randomized patients (561 vs 549 seconds in the placebo group).

• **Exposure to nonrandomized therapy:**

The majority of patients received concomitant diuretic therapy, and increases above pre-treatment diuretic doses were allowed during the randomized study.

▸ **Efficacy outcomes**

Duration of symptom-limited exercise:

The mean change from pre-treatment exercise duration in the digoxin group did not differ significantly from that in the placebo group. The results of an intent-to-treat analysis were not reported.

NYHA class:

No statistically significant mean improvement in NYHA class was observed in either treatment group. The results of an intent-to-treat analysis were not reported.

LVEF:

In the dataset which excluded patients who deviated from randomized therapy, digoxin tended to produce a larger mean increase from pretreatment LVEF (4.4 percentage points) than did placebo (0.9 percentage points; $p < 0.10$). In the intent-to-treat dataset the drugs were statistically distinguishable with respect to their effect on LVEF (4.1 vs 1.3 percentage point change in the digoxin vs placebo groups, respectively; $p < 0.05$).

▸ **Efficacy outcomes** [continued]:

Requirement for increased diuretic dose:

A statistically significantly greater proportion of placebo-treated patients (not further specified) were reported to have been on an increased diuretic dose at the *end* of the study ($p < 0.005$ compared to digoxin-treated patients).

Requirement for hospitalization or ER visit for CHF:

The proportion of patients requiring hospitalization or ER visits for CHF was reportedly statistically significantly greater in the placebo group, relative to the digoxin group ($p < 0.05$). The absolute proportions were not specified, nor were the results of an intent-to-treat analysis reported.

Progressive CHF despite additional diuretic:

Progressive CHF despite additional diuretic therapy occurred in 15% of the placebo-treated patients, and in 4.2% of the digoxin-randomized group ($p < 0.05$). Results of the intent-to-treat analysis were not reported.

COMMENTS (publication of The Captopril-Digoxin Multicenter Research Group):

1. In NYHA class II-III CHF patients in NSR digoxin was reported to be statistically significantly more beneficial than placebo with respect to its effect on the proportion of patients with an increased diuretic dose at the end of the study, and the proportion requiring hospitalization or ER visits for CHF. Digoxin produced no statistically significantly beneficial effect on the duration of symptom-limited exercise, NYHA class, or LVEF [non intent-to-treat].

2. One cannot exclude the possibility that temporary increases above pre-treatment diuretic doses may have confounded this study.

3. A bias towards underestimating the efficacy of digoxin was plausibly introduced by the exclusion of 30 patients whose CHF worsened (during the run-in) following digoxin withdrawal.

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4.2.2 Publication of DiBianco, et. al. (Milrinone-Digoxin Study)

CITATION: DiBianco R, et. al. A comparison of oral milrinone, digoxin, and their combination in the treatment of patients with chronic heart failure. N Eng J Med 1989; 320: 677-683.

SUMMARY:

This placebo-controlled, double-blind, presumably parallel-group, withdrawal study randomized 111 subjects[12] (NYHA class II-III CHF patients in NSR) to 12 weeks of placebo or digoxin (in addition to background diuretic therapy) subsequent to a 4-8 week digoxin-treated run-in. The principle endpoints were the changes from pre-withdrawal duration of symptom-limited exercise, and the proportions requiring additional therapy during the withdrawal.

PROTOCOL:

▸ **Enrollment criteria:**

Included were NYHA class II-III CHF patients in NSR. Excluded were patients with supraventricular arrhythmia, angina, uncorrected valvular disease, and those who required a β-adrenoreceptor antagonist.

▸ **Qualifying criteria:**

Patients qualified for randomization if their CHF stabilized during a 4-8 week digoxin-treated (0.125-0.5 mg/d), and diuretic-treated run-in period, and if they reproducibly exercised for 2-12 minutes (with a modified Naughton treadmill protocol).

▸ **Treatment regimen:**

Qualified patients were randomized to 12 weeks of treatment with digoxin (at the same once-daily dose as given during the run-in), or placebo (in addition to background diuretic therapy at the same dose as used in the run-in).

▸ **Endpoints:**

The efficacy endpoints included the change from pre-withdrawal exercise duration (assessed 1-9 hours after digoxin dosing), the change from pre-withdrawal LVEF, and the proportion of patients who required additional therapy (termed "cointervention").

[12]excluding those exposed to milrinone.

▸ **Statistical procedures:**

• **Dataset analyzed:**

It is not clear which dataset was the source of the reported analysis.

• **Handling of missing data:**

It is not clear how missing data (if any) were handled.

• **Analyses performed:**

For continuous variables, an analysis of variance (ANOVA) was performed. The chi-square statistic was used to compare the proportions requiring addition therapy.

RESULTS:

▸ **Treatment group comparability:**

• **Demographics:**

Neither the proportion of placebo-randomized patients receiving digoxin prior to the study, nor their mean digoxin dose, was reported. The placebo and digoxin treatment groups were comparable with respect to pre-withdrawal mean LVEF, NYHA class, and age, as well as the distribution of sex.

• **Disease severity:**

The placebo and digoxin treatment groups were comparable with respect to pre-withdrawal LVEF.

• **Exposure to nonrandomized therapy:**

It is not clear whether the exposure to nonrandomized therapy was comparable throughout the study.

▸ **Efficacy outcomes:**

Duration of exercise:

The mean change from pre-withdrawal exercise duration after 12 weeks was 66 vs 6 seconds in the digoxin vs placebo-treated groups, respectively ($p = 0.03$).

LVEF:

A statistically significant treatment difference was observed with respect to the mean change from pre-withdrawal LVEF (-2 percentage points in the placebo group and 1.7 percentage points in the digoxin group ($p < 0.01$)).

Requirement for additional therapy:

The treatment groups were also statistically distinguishable with respect to the proportion of patients who required additional therapy (15 vs 47% in the the digoxin vs. placebo-treated groups, respectively ($p < 0.001$)).

Worsening CHF requiring discontinuation:

It was reported that 16% of placebo-treated patients experienced worsening CHF requiring discontinuation, as compared to none of the digoxin-randomized patients. It is not clear whether this assertion only pertains to the first 2 weeks post-withdrawal, as opposed to the entire 12 week withdrawal period.

COMMENTS (publication of DiBianco et. al. (Milrinone-Digoxin):

1. In NYHA class II-III CHF patients in NSR digoxin was reported to be statistically more beneficial than placebo with respect to its effect on mean LVEF (3.7 percentage point treatment difference), and the proportion of patients requiring additional therapy (32 percentage point treatment difference).

2. The digoxin-randomized group manifested a 60 second mean increase from pre-randomization exercise duration, however the digoxin-withdrawn group did not manifest even a trend towards a mean decrease in exercise duration after 12 weeks. Assuming that the digoxin-withdrawn group had been adequately treated prior to randomization, then their post-withdrawal outcome supports the conclusion that digoxin conferred no beneficial effect on exercise. While there are no data that I am aware of which define the minimum duration of digoxin exposure required for the onset of an exercise effect, it is plausible (on the basis of the observed 2-6 week disappearance time for digoxin effect on exercise duration in the RADIANCE and PROVED trials) that the 4-8 weeks of digoxin therapy during the run-in of the Milrinone-Digoxin trial (in addition to any pre-study digoxin exposure) did represent adequate pre-withdrawal treatment.

4.2.3 Publication of The Xamoterol Study Group

CITATION: The German and Austrian Xamoterol Study Group. Double-blind placebo-controlled comparison of digoxin and xamoterol in chronic heart failure. Lancet 1988; 1: 489-93.

SUMMARY:

This placebo-controlled, double-blind, parallel-group study randomized 204 subjects[13] (NYHA class II-III CHF patients, the majority of whom were in NSR) to receive oral digoxin, or placebo for 12 weeks subsequent to a 1 week withdrawal from previous therapies. The objectives were to assess the mean changes from the pre-treatment duration of symptom-limited exercise, and the clinical symptoms of CHF.

PROTOCOL:

- **Enrollment criteria:**

Enrolled subjects were NYHA class II-III CHF patients. Excluded were patients who required ongoing therapy with digitalis, β-adrenoreceptor antagonists, arteriolar vasodilators, ACE inhibitors, calcium antagonists, or antiarrhythmics.

- **Treatment regimen:**

After a 1 week placebo run-in patients were randomized to receive oral digoxin, or placebo for 12 weeks.

- **Endpoints:**

The mean change from the pre-treatment duration of symptom-limited exercise was assessed, however exercise-limiting symptoms were not restricted to those specific for CHF (22% of placebo-randomized and 13% of digoxin-randomized patients stopped exercise on the basis of chest pain). Exercise was performed on a bicycle ergometer starting at 20 watts (W) for the first minute and increasing by 20 W every minute to a maximum of 240 W. Changes from pretreatment symptoms during daily life were measured by the Likert questionnaire, and visual analogue scale.

[13]not including the xamoterol arm.

Publication of The Xamoterol Study Group

▸ **Statistical procedures:**

• **Data set analyzed:**

Approximately 30% of the randomized patients withdrew during the double-blind phase. An analysis of study completers was presented. Data from 2 patients in each group were included in the analyses despite having violated the protocol by increasing their diuretic dose. The numbers of analyzed patients with week 12 exercise data were 72 and 70 in the placebo and digoxin-randomized groups, respectively.

• **Handling of missing data:**

It is not clear how missing data among study completers (if any) were handled.

• **Analyses performed:**

ANCOVA and paired t tests were used to analyze the exercise data.

RESULTS:

▸ **Treatment group comparability:**

• **Demographics:**

The digoxin and placebo-randomized groups were similar with respect to pre-treatment demographic characteristics. Approximately 2% in each group had atrial fibrillation. Half received a cardiac glycoside prior to the study.

• **Exposure to randomized therapy:**

The mean concentration of digoxin was 0.87 ng/ml (therapeutic range 0.7-1.7 ng/ml).

• **Exposure to nonrandomized therapy:**

Concomitant diuretic use was allowed at unchanged doses.

Publication of The Xamoterol Study Group

▸ **Efficacy outcomes:**

Duration of symptom-limited exercise:

Among completers the mean changes from pre-treatment exercise duration were not statistically distinguishable between treatment groups ($p > 0.05$) [the exact p value and the extent of the changes are not discernible]. Twenty two percent of placebo-randomized patients and 13% of digoxin-randomized patients stopped exercise on the basis of chest pain at week 12.

CHF scores:

The proportion of completers with improvement from pre-treatment peripheral edema was 78 vs 44% in the digoxin vs placebo groups, respectively. The proportion with improvement from pre-treatment basal lung crepitance was 88 vs 38% in the digoxin vs placebo groups, respectively. Each of these differences was attributed a nominal p value less than 0.05. The mean changes in several other signs and symptoms of CHF were not statistically distinguishable in the two groups.

Worsening CHF:

The proportion of patients who discontinued because of worsening CHF was 4.0 vs 5.8% in the digoxin vs placebo groups, respectively [p value not reported].

COMMENTS (publication of The Xamoterol Study Group):

1. This study reported only an analysis of the roughly 70% of randomized patients who completed the trial. These results are thus plausibly subject to bias since study discontinuations may not have been independent of outcome or treatment.

2. In NYHA class II-III CHF patients (the majority of whom were in NSR) digoxin was reported to produce no statistically distinguishable effect on exercise duration. This result was plausibly confounded by the inclusion of angina-limited tests (in 22 vs 13% of patients in the placebo vs digoxin-randomized groups, respectively.)

3. Although some physical signs of CHF showed an apparently significant digoxin-related improvement, it is plausible (given the multiplicity of comparisons) that the nominal p values are unreliable.

4.2.4 Publication of Guyatt et. al.:

CITATION: Guyatt et. al. A controlled trial of digoxin in congestive heart failure. Am J Cardiol 1988; 61: 371-375.

SUMMARY:

This placebo-controlled, double-blind, 2-period crossover study analyzed 20 subjects (NYHA class II-III CHF patients in NSR) who received (in random sequence) digoxin, or placebo during each 7 week treatment period. All subjects initially received digoxin during a run-in period. The principal objectives were to assess the proportion who required a treatment intervention, the duration of symptom-limited exercise, the distance walked in 6 minutes, and the signs and symptoms of CHF.

PROTOCOL:

▸ **Enrollment criteria:**

Enrolled were NYHA class II-III CHF patients in NSR who manifested dyspnea-limited exercise.

▸ **Qualifying criteria:**

During a run-in period (of unspecified duration) all patients were given digoxin (titrated to achieve a serum level (at an unspecified time after dose) between 1.54 and 2.56 nmol/L).

▸ **Treatment regimen:**

Patients were randomized to digoxin (at the dose established during the run-in), or placebo during a double-blind, 2-period, sequence-randomized crossover study with 7 week long treatment periods.

▸ **Endpoints:**

The efficacy endpoints were the between-period differences in the duration of symptom-limited bicycle exercise, the distance of a 6 minute walk, the CHF score (measuring dyspnea, lung crepitance, tachycardia, JVD, and radiographic evidence of pulmonary edema), as well as the proportion requiring a treatment intervention ("treatment failures").

▸ **Statistical procedures:**

• **Handling of missing data:**

It is not clear how missing data (if any) were handled.

• **Dataset analyzed:**

The number of randomized subjects is not clear. Of the 23 who completed the study 3 were excluded for protocol violations, and 5 withdrew (1 withdrew because of worsening CHF in each treatment group). It appears that analyses of completers were presented (although this is not entirely clear).

Publication of Guyatt et. al.

▸ **Statistical procedures** [continued]:

• **Analyses performed**:

The data were analyzed according to the crossover procedure of Hills and Armitage.

RESULTS:

▸ **Exposure to randomized therapy**:

The mean digoxin levels were 1.75 ± 0.45 nmol/liter.

▸ **Exposure to nonrandomized therapy**:

It is not clear whether the patients were exposed to background therapies at either fixed or variable doses.

▸ **Efficacy outcomes**:

Duration of symptom-limited exercise:

Thirteen patients exercised during both periods. The mean duration of symptom-limited exercise at the end of week 7 was not statistically distinguishable between treatments (6.4 vs 6.5 minutes during the digoxin vs placebo regimens, respectively ($p > 0.05$).

Walk distance:

The distance of the 6 minute walk (at the end of week 7) was not statistically distinguishable between treatment groups (1356 vs 1294 feet in the digoxin vs placebo groups, respectively; $p = 0.11$).

CHF score:

The mean overall CHF score was significantly lower (signifying less severe CHF) during digoxin treatment than during placebo treatment (2.3 vs 4.4, respectively; $p < 0.05$).

Requirement for treatment intervention:

Based on numerators[14] of 7 vs 0 in the placebo vs digoxin groups, respectively, the proportion requiring treatment intervention was reported to be significantly higher during placebo treatment ($p = 0.03$). However, this analysis did not account for the 1 placebo patient who withdrew because of worsening CHF.

[14]the denominators for the analyzed dataset were not described.

Publication of Guyatt et. al.

COMMENTS (publication of Guyatt et. al.):

1. In NYHA class II-III CHF patients in NSR digoxin was reported to be significantly more beneficial than placebo with respect to its effect on overall CHF score, and the proportion of patients who required a treatment intervention. However, one cannot exclude the possibility that these findings were confounded by increases above pre-treatment diuretic doses.

2. No statistically distinguishable effects of digoxin on exercise duration, or walk distance were observed.

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4.2.5 Publication of Fleg et. al. in 1982

CITATION: Fleg JL, et. al. Is digoxin really important in treatment of compensated heart failure: a placebo-controlled crossover study in patients with sinus rhythm. Am J Med 1982; 73: 244-250.

SUMMARY:

This placebo-controlled, double-blind, 2-period crossover study randomized 40 subjects (NYHA class II-III CHF patients in NSR) to receive (in random sequence) digoxin, or placebo during each 12 week treatment period. The principal objective was to assess the between-period difference in the duration of symptom-limited exercise.

PROTOCOL:

▸ **Enrollment criteria:**

Enrolled subjects were NYHA class II-III CHF patients in NSR. The majority of the efficacy-analyzed subjects (87%) were receiving digoxin therapy prior to the study (mean dose 0.24 mg/d).

▸ **Qualifying criterion:**

Before randomization the digoxin dosage was adjusted to achieve a therapeutic serum level of 1.0 to 2.0 ng/ml at least six hours after the last dose.

▸ **Treatment regimen:**

Patients received digoxin (presumably at the same dose which was administered during the run-in), or placebo, in random sequence, during 12 week treatment periods. The dosages of all other cardiovascular medications were to be held constant.

▸ **Endpoints:**

The principal efficacy endpoint was the between-period difference in the duration of symptom (fatigue, dyspnea, or *angina*)-limited treadmill exercise (modified Balke protocol).

▸ **Statistical procedures:**

• **Dataset analyzed:**

Thirty patients were efficacy-analyzed. Ten patients were excluded for the following reasons: subtherapeutic serum digoxin levels, aortic valvular insufficiency, and pneumonia.

• **Handling of missing data:**

It is not clear how missing data (if any) were handled.

• **Analyses performed:**

The data were analyzed by means of a paired, two-sided t test.

RESULTS:

▸ **Exposure to nonrandomized therapy:**

The proportion of patients taking concomitant diuretics, long-acting nitrates, and β-adrenoreceptor antagonists was 58, 13, and 10%, respectively.

▸ **Efficacy outcomes:**

Duration of symptom-limited exercise:

In the 12 subjects who performed exercise during both periods no statistically significant difference in mean symptom-limited exercise duration was observed (7.6 versus 7.8 minutes during the digoxin vs placebo regimens, respectively). Three of the exercise tests were limited by angina.

Worsening CHF:

Among the subset of patients who had received digoxin therapy prior to the study, no worsening of CHF was observed during digoxin withdrawal. No results were described for other datasets.

Requirement for additional therapy:

During placebo administration it was not necessary to alter the doses of concomitant therapies or to intervene with additional therapies. Information of this type was not presented for patients receiving randomized digoxin treatment.

COMMENTS (publication of Fleg et. al. in 1982):

1. This study adds little to our knowledge of digoxin's effects in CHF. In NYHA class II-III CHF patients in NSR digoxin was reported to produce no statistically significant benefit with respect to exercise duration. However, the design of the exercise endpoint was flawed in that it failed to exclude patients with angina-limited exercise.

4.2.6 Publication of Fleg et. al. in 1991

CITATION: Fleg JL, et. al. Effect of maintenance digoxin therapy on aerobic performance and exercise left ventricular function in mild to moderate heart failure due to coronary artery disease: a randomized, placebo-controlled, crossover trial. J Am Coll Cardiol 1991; 17: 743-751.

SUMMARY: This placebo-controlled, double-blind, 2-period crossover study randomized 10 subjects (NYHA class II-III CHF patients in NSR) to receive (in random sequence) digoxin, or placebo during 4 week treatment periods. Subjects had received prior treatment with digoxin and diuretics. The principal objectives were to assess the between-period difference in the duration of symptom-limited exercise, and the exercise LVEF.

PROTOCOL:

▸ **Enrollment criteria:**

Enrolled subjects were NYHA class II-III CHF patients in NSR with LVEF < 50%, and CHF secondary to coronary artery disease (CAD), but without angina-limited exercise.

▸ **Qualifying criterion:**

Before randomization the digoxin dosage was adjusted to achieve a serum level of 1-2 ng/ml at least 6 hours after the previous dose.

▸ **Treatment regimen:**

Patients received digoxin (presumably at the same dose which was administered during the run-in), or placebo (in random sequence) during each 4 week treatment period.

▸ **Endpoints:**

The principal efficacy endpoint was the between-period difference in the duration of symptom (fatigue or dyspnea)-limited treadmill exercise (modified Balke protocol). Radionuclide exercise (upright bicycle) LVEF was assessed with the data interpreted by a single scintigram reader.

▸ **Statistical procedures:**

-- • **Dataset analyzed:**

Twelve patients were enrolled, and 2 were excluded from the efficacy analysis after dropping out (one with worsening CHF during placebo therapy).

Publication of Fleg et. al.-1991

• **Handling of missing data:**

It is not clear how missing data (if any) were handled.

• **Analyses performed:**

The data were analyzed by means of a paired, two-tailed t test.

RESULTS:

▸ **Exposure to randomized therapy:**

The mean randomized digoxin dose was 0.28 mg/d, and the mean serum digoxin level was 1.4 ng/ml.

▸ **Exposure to nonrandomized therapy:**

All patients were receiving background diuretic therapy and five were receiving a vasodilator. None of the 10 patients required changes in the diuretic or vasodilator doses.

▸ **Efficacy outcomes:**

Duration of symptom-limited exercise:

The mean duration of symptom-limited exercise did not significantly differ after 4 weeks (7.7 vs 7.3 minutes during digoxin vs placebo-treatment, respectively; $p > 0.05$).

LVEF:

Exercise LVEF was significant higher during digoxin treatment than during placebo (31.9 vs 27.2%, respectively; $p < 0.05$).

COMMENTS (publication of Fleg et. al. in 1991):

1. In NYHA class II-III CHF patients in NSR digoxin was reported to produce no statistically distinguishable effect on the duration of symptom-limited exercise, but to have a significantly more beneficial impact on mean LVEF than did placebo (4.7 percentage point difference). However, the reliability of the LVEF data is reasonably questioned since no measures were used (e.g. the use of a panel of scintigram interpreters) to minimize the widely recognized effect of observer bias.

4.2.7 Publication of Lee et. al.:

CITATION: Lee DC, et. al. Heart failure in outpatients: a randomized trial of digoxin versus placebo. N Eng J Med 1982; 306: 699-705.

SUMMARY:

This placebo-controlled, double-blind, 2-period crossover study randomized 35 subjects (NYHA class I-III CHF patients in NSR) to receive (in random sequence) digoxin, or placebo during treatment periods of approximately 9 weeks duration. The principal objectives were to assess between-period differences in signs and symptoms of CHF, LVEF, and echocardiographic LVED diameter.

PROTOCOL:

▸ **Enrollment criteria:**

Enrolled were patients with either persistent or *episodic* CHF (NYHA class I-III) who were in NSR.

▸ **Treatment regimen:**

During a run-in period (of unspecified duration) the diuretic (present as background therapy in the majority of patients) was dose-optimized. Subjects were then randomized to receive digoxin or placebo during each of two periods of approximately 9 weeks duration [the authors report only that treatment periods were "usually" nine weeks long]. If CHF worsened the treatment period was terminated and the patient was administered digoxin for an unspecified duration of time before crossing over to the alternative randomized therapy.

▸ **Endpoints:**

The principal endpoint was the between-period difference in CHF score (which included measures of dyspnea, lung crepitance, tachycardia, JVD, and radiographic evidence of pulmonary edema). Resting radionuclide LVEF, and echocardiographic LVED diameter were also evaluated. Comparisons were made at times "considered representative of each period." These times were reported to be "generally at or near the end of the period".

Publication of Lee et. al.

▸ **Statistical procedures:**

• **Dataset analyzed:**

Ten of the 35 randomized patients were withdrawn (for reasons of sudden death, acute pulmonary edema, acute MI, and noncompliance).

• **Handling of missing data:**

It is not clear how missing data (if any) were handled.

• **Analyses performed:**

Group means were analyzed using the Student's t-test, and proportions were analyzed by means of Fishers exact test. The Wilcoxin signed-rank test was used to analyze between-period changes in CHF scores. The Bonferroni correction was applied to multiple comparisons.

RESULTS:

▸ **Demographic characteristics:**

All but one patient had been treated with digoxin at the time of study enrollment.

▸ **Exposure to randomized therapy:**

The mean daily digoxin dose was 0.435 mg (titrated to a 24 hour post-dose serum level of 1.2 ng/mL).

▸ **Exposure to nonrandomized therapy:**

The majority (88%) of the efficacy-analyzed patients received concomitant diuretics, and six also received vasodilators.

Publication of Lee et. al.

▸ **Efficacy outcomes:**

CHF score:

There was a statistically significantly lesser overall severity of CHF signs and symptoms during digoxin therapy (mean score of 3.6 vs 2.0 during placebo treatment; $p < 0.05$).

LVEF:

Resting LVEF was not statistically distinguishable between the treatment groups (29 vs 30% in the placebo vs digoxin groups, respectively; $p = 0.49$).

LVED diameter:

LVED diameter was statistically significantly smaller during digoxin therapy (31 mm/m^2) than during placebo therapy (33 mm/m^2; $p = 0.003$).

COMMENTS (publication of Lee, et. al.):

1. There were reported beneficial effects of digoxin on overall CHF score, and LVED diameter in NYHA class I-III CHF patients in NSR. However, this study was plausibly confounded by spontaneous changes in disease severity (some patients with episodic CHF were enrolled), and the treatment comparisons were made at times that were not prespecified. The findings cannot therefore be considered convincing.

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4.2.8 Publication of Taggart et. al.

CITATION: Taggart AJ, et. al. Digoxin withdrawal after cardiac failure in patients with sinus rhythm. J Cardiovasc Pharmacol 1983; 5: 229-234.

SUMMARY:

This placebo-controlled, double-blind, 2-period crossover, withdrawal study randomized 22 subjects (NYHA class I-III CHF patients in NSR) to receive (in random sequence) digoxin, or placebo during treatment periods of 12 weeks duration. The principal objective was to assess between-period differences in symptoms of CHF.

PROTOCOL:

▸ **Enrollment criteria:**

This study enrolled NYHA class I-III chronic CHF patients who were in NSR and who had plasma digoxin concentrations of 0.8-2.5 ng/ml (1.0-3.2 nmol/L).

▸ **Treatment regimen:**

All patients had been treated with digoxin at the time of study enrollment. Each was randomized to receive digoxin (at their usual daily dose) or placebo during each of two sequence-randomized crossover periods of 12 weeks duration.

▸ **Endpoints:**

The principal objective was to assess between-period differences in symptoms of CHF (using a scoring system based on the NYHA functional classification).

▸ **Statistical procedures:**

• **Dataset analyzed:**

Three patients were excluded from the efficacy analysis after withdrawing with worsened CHF (two had received placebo and one had been randomized to digoxin).

• **Handling of missing data:**

It is not clear how missing data (if any) were handled.

• **Analyses performed:**

Statistical analyses utilized Student's paired t test, Fisher's exact probability test, the Mann-Whitney U test, and Wilcoxin's signed rank test.

Publication of Taggart et. al.

RESULTS:

▸ **Demographic characteristics:**

All patients had been treated with digoxin at the time of study enrollment.

▸ **Exposure to randomized therapy:**

The mean plasma digoxin concentration during randomized treatment was 1.2 ng/ml (1.5 nmol/L). None of the patients had detectable plasma levels of digoxin during the placebo phase.

▸ **Exposure to nonrandomized therapy:**

It is not clear whether the patients were exposed to background therapies at either fixed or variable doses.

▸ **Efficacy outcomes:**

CHF score:

Overall CHF scores were not statistically distinguishable in the two treatment groups (12.1 vs 12.9 in the digoxin vs placebo groups, respectively; $p > 0.05$).

Worsening CHF:

Four patients manifested a deterioration of CHF during placebo therapy, and two did so during randomized digoxin treatment ($p > 0.05$). Those who deteriorated on placebo did so within 3-8 weeks after digoxin withdrawal.

COMMENTS (publication of Taggart, et. al.):

1. In NYHA class I-III CHF patients in NSR digoxin was reported to produce no statistically significantly beneficial effect on overall CHF score, or the proportion of patients whose CHF clinically deteriorated. It is unknown whether there were confounding increases in diuretic doses occurred.

4.2.9 Publication of Pugh, et. al.

CITATION: Pugh SE, et. al. Clinical, haemodynamic, and pharmacologic effects of withdrawal and reintroduction of digoxin in patients with heart failure in sinus rhythm after long term treatment.

SUMMARY:

This placebo-controlled, double-blind, 2-period crossover study evaluated 44 subjects (stable CHF patients in NSR) who received digoxin, or placebo during sequence-randomized treatment periods of 8 weeks duration. All of the patients had been receiving digoxin at the time of initiation of the study. The objectives were to assess between-period differences in CHF signs and symptoms, LVED diameter, and the proportion with a deterioration in symptom-limited exercise "capacity" [defined below].

PROTOCOL:

- **Enrollment criteria**:

This study enrolled stable CHF patients in NSR who had been taking digoxin for at least three months (with a steady state plasma digoxin concentration ≥ 0.8 ng/mL (1.0 nmol/L).

- **Treatment regimen**:

Subjects were randomized to receive digoxin (at their usual daily dose), or placebo during each of two crossover periods of 8 weeks duration.

- **Endpoints**:

The efficacy endpoints were the between-period differences in CHF signs and symptoms, LVED diameter, and the proportion of patients with a deterioration in symptom-limited exercise "capacity." A deterioration in exercise "capacity" was defined as the development of dyspnea within 10 minutes of exercise at a workload which (prior to randomization) did not induce dyspnea within 10 minutes of exertion. There was no assessment of the reproducibility of the pre-randomization workload associated with the absence of dyspnea.

CHF scores were based on an assessment of third heart sound, JVD, hepatomegaly, pulmonary and peripheral edema, cardiac rhythm, orthopnea, paroxysmal nocturnal dyspnea, ability to climb stairs, distance walked, NYHA class, and palpitations. Clinical deterioration of CHF was defined as a "consistent" [this term was undefined] increase in total score of at least two points, one of which had to be attributable to a worsening sign. A total score of 12 was normal, and maximal dysfunction was given a score of 35.

Echocardiographic measures of LVED diameter were obtained by conventional methodology.

▸ **Statistical procedures:**

• **Data set analyzed:**

Although the manuscript reports on the results of 44 subjects, it is not clear how many were randomized or how many dropped out.

• **Handling of missing data:**

It is not clear how missing data (if any) were handled.

• **Analyses performed:**

Statistical analyses utilized Wilcoxin's rank sum test, Student's t test, one way ANOVA, and Tukey's test. The specific applications of these procedures were not described.

RESULTS:

▸ **Demographics:**

The majority (61%) had an ischemic etiology of CHF.

▸ **Exposure to randomized therapy:**

Randomized digoxin doses appeared to have been titrated in order to maintain a steady state plasma digoxin concentration ≥ 0.8 ng/mL (1.0 nmol/L).

▸ **Exposure to nonrandomized therapy:**

The majority (75%) were receiving background diuretic therapy, and the proportion receiving concomitant β-adrenoreceptor antagonists vs vasodilators was 20 vs 9%, respectively. Dosages of diuretics were increased during periods of deterioration.

Publication of Pugh et. al.

▸ **Efficacy outcomes:**

Deterioration in symptom-limited exercise "capacity":

By the eighth week of placebo therapy there were apparently no cases of deterioration in symptom-limited exercise "capacity." The results during randomized digoxin therapy were not described).

Worsening CHF:

Worsening CHF was manifest in 25% of placebo-receiving patients and 11% of digoxin-randomized patients ($p = 0.02$ after exclusion of patients whose worsening involved the development of atrial fibrillation).

LVED diameter:

There were no statistically significant mean changes in LVED diameter.

COMMENTS (publication of Pugh, et. al.):

1. In stable CHF patients in NSR digoxin was reported to be statistically distinguishable from placebo with respect to its effect on the proportion of patients with worsening CHF (mean 14 percentage point difference). Digoxin was reported to produce no significantly beneficial effect on LVED diameter.

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4.2.10 Preliminary publication (abstract) of Drexler, et. al.

CITATION: Drexler H, et. al. Effect of captopril and digoxin on quality of life and clinical symptoms in patients with coronary artery disease and mild heart failure [abstract]. J Am Coll Cardiol 1992; 19:260A.

SUMMARY: This placebo-controlled, double-blind, presumably parallel-group study randomized 133 subjects[15] (NYHA class II-III CHF patients) to receive digoxin, or placebo for 1 year. The endpoints included changes from pre-treatment NYHA class, and duration of bicycle exercise. This publication was a preliminary report of the CADS Study Group.

PROTOCOL: One can only discern that enrolled patients had histories of MI and CHF, and that patients were randomized to either digoxin or placebo for 1 year. Statistical procedures were not characterized.

RESULTS:

- **Demographics**:

Pretreatment demographic characteristics were comparable (including LVEF, NYHA class, age, infarct location, and prevalence of angina).

- **Efficacy outcomes**:

Duration of symptom-limited exercise:

No statistically significant treatment effect on the change from pre-treatment exercise duration was observed.

NYHA class:

At an unspecified timepoint there was statistically significant improvement from pre-treatment NYHA class in 46% of digoxin-randomized patients and 28% of placebo-treated patients ($p < 0.05$).

CHF score:

After one year of therapy there was reported to be statistically significant improvement from pre-treatment scores of general well-being and symptom scores in digoxin-randomized patients ($p < 0.05$ vs placebo).

COMMENTS (published abstract of Drexler, et. al.):

1. No rigorous analysis of this preliminary publication can be made.

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[15]not including the captopril arm.

5 Safety:

5.1 Database and methodology used for the safety analysis:

The database presented in the sponsor's safety assessment was comprised of 4 placebo-controlled, parallel-group studies, each of which randomized 88-196 NYHA class II-III CHF patients (studies 437, 436, DiBianco et. al. (the Milrinone-Digoxin Study), and the Captopril-Digoxin Multicenter Research Group study). In each study the randomized treatment was 12 weeks in duration, except for the 24 week long Captopril-Digoxin Study. Cases of worsening CHF were excluded from the safety analysis since these were analyzed as efficacy endpoints.

For study 437 the AE data from the second week of the withdrawal were excluded from the treatment group comparison in an attempt to reduce any confounding effect which may have been introduced by digoxin carryover.

5.2 Drug exposure:

In the 437 and 436 Studies, the mean dose of digoxin was 0.38 mg/d. In the Milrinone-Digoxin Study the mean digoxin dose was 0.21 mg/d, and it was not reported in the Captopril-Digoxin Study.

5.3 Deaths:

These studies were underpowered the assessment of the effect of digoxin on survival. The crude proportions of subjects who died during randomized treatment are shown below. Narrative summaries of deaths begin on the next page.

Table 7:

Crude proportion of deaths in digoxin-randomized patients (intent-to-treat)

study	*placebo*	*digoxin*
436 & 437	2.2% (3/139)	3.9% (5/127)[16]
Milrinone-Digoxin	6.1%	4.8%
Captopril-Digoxin	6.0%	7.3%

[source: modification of table 29, page 266, vol 1.26]

[16]if one excludes the patient who died 5 days after completing randomized digoxin therapy, the crude proportion of deaths is 3.1% in this treatment group.

5.3 **Deaths** [continued]:

Narratives for deaths among patients exposed to digoxin in studies 436 & 437:

Patients receiving *randomized* digoxin:

Patient 436-5397 was a 66 year old male who was admitted to the hospital with chest pain, and subsequently arrested and died of probable acute MI.

Patient 437-6215 was a 69 year old male who died of ventricular fibrillation during an acute MI.

Patient 437-6298 was a 70 year old male who died soon after sustaining head trauma (CAD was found at autopsy).

Patient 437-6517 was a 54 year old male who arrived dead to an ER after complaining of chest pain (presumably having sustained an MI).

Patient 437-6220 was a 64 year old male who was found dead 5 days after completing randomized digoxin therapy. The cause of death was an acute MI.

Patients receiving *nonrandomized* digoxin:

Patient 436-1472 was a 77 year old male who died of acute MI.

Patient 436-1451 was a 64 year old female whose unwitnessed death was attributed to "natural causes."

Patient 437-2719 was a 73 year old male who succumbed to sudden death.

Patient 437-2542 was a 78 year old male who died of cardiorespiratory arrest.

Patient 437-2244 was a 55 year old male who died of acute MI with cardiac arrest.

Patient 437-2339 was a 62 year old male with sudden death.

Patient 437-2340 was a 57 year old male who was found unresponsive and appeared to have sudden death (although it was reported to be a death of undetermined cause).

Deaths in the Captopril-Digoxin and Milrinone-Digoxin studies:

In the Captopril-Digoxin Study, there were 6 deaths in the placebo group and 7 in the digoxin group. In the Milrinone-Digoxin Study (DiBianco, et.al) 3 patients in the placebo group and 3 in the digoxin group died during the withdrawal period (all cardiac deaths).

5.4 Serious or potentially serious AE:

In study 436, during the withdrawal period 4 placebo-treated patients, and 6 digoxin-treated patients had serious AE (other than death or worsening CHF, which were evaluated as efficacy endpoints). Most common were myocardial ischemia (occurring in one placebo patient, and three digoxin patients), and AF (occurring in two placebo patients, and no digoxin patients).

In study 437, during the withdrawal period 15 patients in the placebo group and 10 patients in the digoxin group had serious AE other than death or worsening CHF. Most common were myocardial ischemia (occurring in four placebo patients and two digoxin patients), cerebrovascular events (occurring in one placebo patient and two digoxin patients), and AF (occurring in two placebo patients and no digoxin patients).

In studies 437 and 436, one of 127 patients randomized to digoxin (0.8%) developed digoxin toxicity. No episodes of digoxin toxicity were reported in the published reports of the Milrinone-Digoxin Study or the Captopril-Digoxin Study.

5.5 Dropouts:

In study 436, no digoxin-randomized patients dropped out for reasons other than treatment failure or death (endpoints which were evaluated in the efficacy analysis). Fifteen patients discontinued from nonrandomized digoxin therapy for reasons other than death. Two thirds of these dropouts were associated with cardiovascular AEs (heart block, AF, ventricular tachycardia, hypertension, angina, and worsening heart failure).

In study 437, two digoxin-randomized patients dropped out for reasons other than treatment failure or death (one with acute MI, and the other with digoxin toxicity). Ten patients discontinued from nonrandomized digoxin treatment for reasons other than death. Sixty percent of these dropouts were associated with cardiovascular AEs (AF, angina, and worsening heart failure) and one was on the basis of digoxin toxicity.

In the Captopril-Digoxin Study, no patients in the placebo group and four patients in the digoxin group withdrew from the study because of AE (orthostatic hypotension was noted in the one case which was described in any detail).

In the Milrinone-Digoxin Study (DiBianco, et.al) one digoxin-randomized patient withdrew because of diarrhea.

5.6 Common adverse events

The table below depicts the AE for which the number of reports among digoxin-randomized patients exceeded the number of reports among placebo-randomized patients by at least two. Several of the AEs appearing in this table are not included in the Lanoxin® product label (these new AE were: pain, cough increased, anxiety, myocardial infarct, sinusitis, ear pain, urinary infection, flu-like illness, and hypotension).

Table 8:

Numbers of AE for which the reports among digoxin-randomized patients exceeded the reports among placebo-randomized patients by at least two

Studies	AE	Placebo [n=125]	Digoxin [n=123]
436 & 437			
	cough increased	4	8
	pain	4	7
	abnormal vision	0	4
	diarrhea	1	4
	anxiety	1	4
	nausea	2	4
	myocardial infarct	0	2
	sinusitis	0	2
	ear pain	0	2
	urinary infection	0	2

Only AE occurring during weeks 2-12 of the withdrawal were counted in the above tabulation.

Study	AE	Placebo [n=49]	Digoxin [n=62]
DiBianco			
	diarrhea	1	7
	flu-like illness	0	3
	lightheadedness	0	3
	headache	1	3

Study	AE	Placebo [n=100]	Digoxin [n=96]
Capto-Dig Study			
	"dizziness" or lightheadedness	7	11
	nausea	3	7
	rash	2	4
	palpitation	1	3
	hypotension	0	2

[source: modifications of tables 25-27, pages 6947-6952, vol 1.26]

5.7 Laboratory findings:

In study 436 the observed abnormalities in laboratory measurements were generally of no great clinical importance. However, during the withdrawal period one digoxin-randomized patient had hyperkalemia (serum potassium level of 5.7 mEq/L, but without followup), and one digoxin-randomized patient had a significantly increased SGOT (approximately 2 times normal), but there was no follow up. One patient in each group had serum BUN values more then 25% above the normal range.

In study 437 the observed abnormalities in laboratory measurements were generally of no great clinical importance. However, during the withdrawal period 2 digoxin-randomized and 4 placebo-randomized patient had BUN values more then 25% above the normal range (in some cases clearly associated with worsening CHF). There were also a few cases of transient, mild serum creatinine elevations, and transient, mild hypokalemia among digoxin-randomized patients.

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6. OVERVIEW OF EFFICACY:

Table 9:

Reported placebo-corrected (PC) effects &/or stat significance of PC effects of digoxin in CHF trials

trial	*comments*	*Exercise duration (s)*	*Walk distance (ft)*	*Rx failures (percent-age points)*	*Over all CHF score*	*NYHA class*	*LVEF (percent-age points)*	*LVED diam (various units)*
437	10-12 week withdrawal results; lowest rank assigned to Rx failures	45.5*	125*	-17*	non-signif	signif benefit *	3.6*	-2.2* mm
436	10-12 week withdrawal results; lowest rank assigned to Rx failures	100.5*	19.5	-20*	non-signif	non-signif	5.1*	-1.7 mm
Capto-Dig	plausible bias towards underestimated digoxin effects	non-signif	--	*	--	non-signif	3.5	--
Milrin-Dig	exercise results unconvincing since no post-withdrawal deterioration in placebo group	60.0*	--	-32*	--	--	3.7*	--
Xamot	completers analysis only; exercise plausibly confounded by angina-limited tests	non-signif	--	--	--	--	--	--
Guyatt	unknown whether confounded by increases in diuretics	non-signif	63.3	signif benefit*	signif ben-efit*	--	--	--
Fleg '82	potential confounding by angina-limited exercise tests	-12	--	--	--	--	--	--
Fleg '91	LVEF data plausibly subject to observer bias	24	--	--	--	--	4.7*	--
Lee	included patients with episodic CHF	--	--	--	signif ben-efit*	--	1.0	-2.0* mm/m^2
Taggart	unknown whether confounded by increases in diuretics	--	--	non-signif	non-signif	--	--	--
Pugh	none	--	--	-14*	--	--	--	non-signif

[source: data presented elsewhere in this review]

Statistically significant ("signif") differences from placebo are denoted by asterisks ($p \leq 0.05$). Treatment (Rx) failures are defined either as requiring additional therapy, manifesting worsening CHF, or a combination of these 2 endpoints plus death. Where "*" or "--" are shown without data, this indicates either that no data or no readily summarized data are available [see main body of report for details]. "nonsignif"= statistically nonsignificant ($p \geq 0.05$); "Rx"= treatment.

7. CONCLUSIONS:

a. The previously published, randomized, placebo-controlled trials (herein reviewed) provided reproducible evidence of the statistically significant clinical benefits of digoxin, with respect to the reduction of CHF treatment failures, and the improvement of overall CHF symptom scores in patients in NSR. Within the limits of withdrawal design the RADIANCE and PROVED trials, by demonstrating an increased requirement for treatment interventions in patients withdrawn from oral digoxin, extend this knowledge by supporting the inference that digoxin reduces the requirement for treatment interventions even when CHF patients have been previously stabilized on ACE inhibitors and/or diuretics.

b. None of the published trials herein reviewed provided convincing evidence of a beneficial effect of digoxin on the duration of symptom-limited exercise. In the Milrinone-Digoxin study, the digoxin-randomized group manifested a 60 second mean increase from pre-randomization exercise duration, however the digoxin-withdrawn group did not manifest even a trend towards a mean decrease in exercise duration after 12 weeks. Assuming that the digoxin-withdrawn group had been adequately treated prior to randomization, then their post-withdrawal outcome supports the conclusion that digoxin conferred no beneficial effect on exercise. While there are no data that I am aware of which define the minimum duration of digoxin exposure required for the onset of an exercise effect, it is plausible (on the basis of the observed 2-6 week disappearance time for digoxin effect on exercise duration in the RADIANCE and PROVED trials) that the 4-8 weeks of digoxin therapy during the run-in of the Milrinone-Digoxin trial (in addition to any pre-study digoxin exposure) did represent adequate pre-withdrawal treatment.

The RADIANCE and PROVED trials, by demonstrating (within the limits of withdrawal design) the clinical deterioration of symptom-limited exercise duration in patients withdrawn from digoxin, support the inference that oral digoxin improves exercise duration in NYHA class II-III CHF patients in NSR who are stabilized on ACE inhibitors and/or diuretics.

c. Analyses of efficacy-demographic or safety-demographic interactions in the RADIANCE and PROVED trials have not been submitted, but the power of such analyses would not be reasonably expected to be great.

8. RECOMMENDATIONS:

a. Assuming that the bioequivalence of the clinical trial formulation and the new formulation is validated, I recommend approval of this NDA with revision of current labelling. It should be stated in labelling that:

i. Two large placebo-controlled withdrawal studies, by demonstrating a deterioration of symptom-limited exercise duration, and an increased requirement for CHF treatment interventions in patients withdrawn from digoxin, support the inference (within the limits of withdrawal design) that oral digoxin improves exercise duration and reduces the requirement for CHF treatment interventions in NYHA class II-III CHF patients in NSR who are stabilized on ACE inhibitors and/or diuretics.

ii. following the discontinuation of digoxin in patients receiving ACE inhibitors and/or diuretics the clinical deterioration in the duration of symptom-limited exercise can be gradual, and it is progressive.

b. I recommend against approval of the sponsor's request for marketing exclusivity for Lanoxin® in CHF. Although it is my view that the RADIANCE and PROVED studies provide useful new observations about digoxin's effect on symptom-limited exercise duration, the longstanding absence of evidence of exercise efficacy would, by current division standards, represent a deficiency great enough to support a decision for marketing nonapproval.

Steven M. Rodin, MD

Steven M. Rodin, MD
Medical Officer

1/25/94
Date

cc: RFenichel/HFD-110; GBuehler/HFD-110; HFD-110 division file (NDA 20-405); *no copy to SRodin

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Steven M. Rodin, M.D.
Medical Officer

Food and Drug Administration

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FEB 15 1994

Medical Review of NDA- Addendum #1

1 General information

NDA #:	**20-405**
Drug:	**Digoxin** (Lanoxin®)
Sponsor:	Burroughs Wellcome Company
Date of NDA review:	25 January 1994
Reviewer:	Steven M. Rodin, M.D.
Addendum last revised:	14 February 1994

2 Citation of publication of Pugh, et. al.:

The complete citation for the publication of Pugh SE, et. al. is:

Pugh SE, et. al. Clinical, haemodynamic, and pharmacologic effects of withdrawal and reintroduction of digoxin in patients with heart failure in sinus rhythm after long term treatment. Br Heart J 1989; 61:529-539.

3 Revision of Recommendation "b"

On reconsideration I withdraw the previously offered recommendation "b" [page 56 of my NDA review]. My view is that the sponsor has caught up to current standards of approval by submitting previously absent evidence of digoxin effect on exercise tolerance in CHF. It is the integration of expert legal opinion which I recommend, in order to determine whether the timeframe and nature of this "catch up" entitles the sponsor to marketing exclusivity.

Steven M. Rodin MD 2/14/94

Steven M. Rodin, MD Date
Medical Officer

cc: RFenichel/HFD-110; GBuehler/HFD-110; HFD-110 division file (NDA 20-405); *no copy to SRodin

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20405

CHEMISTRY REVIEW(S)

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-405 **CHEM. REVIEW #:** 1 **REVIEW DATE:** 17-Nov-93

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	30-Sep-93	30-Sep-93	04-Oct-93

NOV 29 1993

NAME & ADDRESS OF APPLICANT: BURROUGHS WELLCOME CO.
3030 Cornwallis Road
Research Triangle Park, NC 27709

Contact person (CMC section): Mr. Wayne Talton
Drug Regulatory Affairs
919-248-8548

DRUG PRODUCT NAME

Proprietary: LANOXIN Tablets
Nonproprietary/USAN: Digoxin
Code Name/#: CAS - 20830-75-5
Alternate names: 38U
38U57
Rougoxin
Chloroformic Digitalin
Homolle's Digitalin
Digacin
Lanicor
12β-Hydroxydigitoxin
Cordioxil
Davoxin
Dixina
Lanocardin
Dilanacin

Chem.Type/Ther.Class: 3 S, 7 S

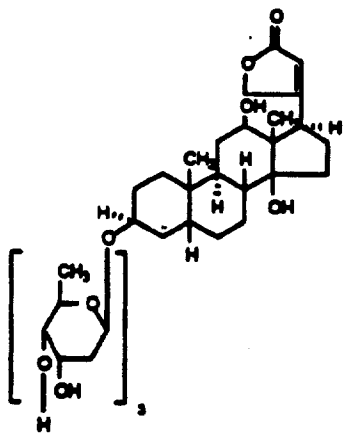
ANDA Suitability Petition/DESI/Patent Status:

Three (3) year marketing exclusivity for Lanoxin (digoxin) Tablets is requested.

PHARMACOL.CATEGORY/INDICATION: Treatment of heart failure in patients receiving angiotensin converting enzyme (ACE) inhibitors and diuretics or diuretics alone.

DOSAGE FORM: Tablets
STRENGTHS: 62.5, 125, 187.5, 250, 375, and 500 μg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: X Rx ____ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Chemical name(s):

3β-[(*O*-2,6-Dideoxy-β-*D*-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β-card-20(22)-enolide (IUPAC)

(3β,5β,12β)-3-[(*O*-2,6-Dideoxy-β-*D*-*ribo*-hexapyranosyl-(1→4)-*O*-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl)oxy]-12,14-dihydroxycard-20(22)-enolide (Chem. Abstr.)

Molecular Formula: $C_{41}H_{64}O_{14}$ Molecular Weight: 780.95

SUPPORTING DOCUMENTS:

NDA 9-330 LANOXIN Injection
NDA 18-118 LANOXICAPS

RELATED DOCUMENTS (if applicable):

CONSULTS:

REMARKS/COMMENTS:

Foreign countries in which Lanoxin products (tablets, injections, injections for infants, elixir) are registered and marketed: Angola, Argentina, Australia, Bangladesh, Belgium, Bolivia, Brazil, Canada, Chile, Costa Rica, Curacao, Cyprus, Denmark, Egypt, Ethiopia, Finland, Germany, Greece, Guatemala, Holland, Hong Kong, Iceland, Indonesia, Iraq, Israel, Italy, Jamaica, Jordan, Kenya, Kuwait, Lebanon, Luxembourg, Malaysia, Mexico, New Zealand, Norway, Oman, Pakistan, Paraguay, Philippines, Portugal, Saudi Arabia, Singapore, South Africa, Spain, Sri Lanka, Sweden, Switzerland, Syria, Taiwan, Thailand, Trinidad, United Arab Emirates, United Kingdom, Uruguay, Yemen Arab Republic, and Zambia.

EER was requested on 11/16/93.

Expiration date - 36 months in HDPE containers and blister packs.

Method validation will be requested to be performed by DDA only.

CONCLUSIONS & RECOMMENDATIONS:

Additional information is requested.

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig. NDA 20-405
HFD-110/Division File
HFD-110/CunninghamD/11/17/93
HFD-100/CSO
District
HFD-102/CKumkumian [#1 only]
R/D Init by: SUPERVISOR

Danute G. Cunningham, Review Chemist
filename: 20405R01.NDA

11-29-93

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

AUG 24 1994

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-405 **CHEM. REVIEW #:** 2 **REVIEW DATE:** August 23, 1994

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	30-Sep-93	30-Sep-93	04-Oct-93
AMENDMENTS	25-May-94	27-May-94	01-Jun-94
	08-Aug-94	10-Aug-94	12-Aug-94

NAME & ADDRESS OF APPLICANT:

BURROUGHS WELLCOME CO.
3030 Cornwallis Road
Research Triangle Park, NC 27709

Contact person (CMC section): Mr. Wayne Talton
Drug Regulatory Affairs
919-248-8548

DRUG PRODUCT NAME

Proprietary: LANOXIN Tablets
Nonproprietary/USAN: Digoxin
Code Name/#: CAS - 20830-75-5
Alternate names: 38U
38U57
Rougoxin
Chloroformic Digitalin
Homolle's Digitalin
Digacin
Lanicor
12β-Hydroxydigitoxin
Cordioxil
Davoxin
Dixina
Lanocardin
Dilanacin

Chem.Type/Ther.Class: 3 S, 7 S

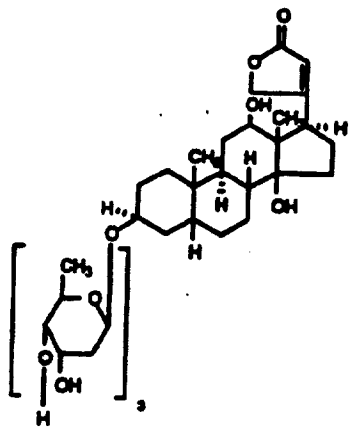
ANDA Suitability Petition/DESI/Patent Status:

Three (3) year marketing exclusivity for Lanoxin (digoxin) Tablets is requested.

PHARMACOL.CATEGORY/INDICATION: Treatment of heart failure in patients receiving angiotensin converting enzyme (ACE) inhibitors and diuretics or diuretics alone.

DOSAGE FORM: Tablets
STRENGTHS: 62.5, 125, 187.5, 250, 375, and 500 μg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: __X__ Rx _____ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Chemical name(s):

3β-[(*O*-2,6-Dideoxy-β-*D*-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β-card-20(22)-enolide (IUPAC)

(3β,5β,12β)-3-[(*O*-2,6-Dideoxy-β-*D*-*ribo*-hexapyranosyl-(1→4)-*O*-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl)oxy]-12,14-dihydroxycard-20(22)-enolide (Chem. Abstr.)

Molecular Formula: $C_{41}H_{64}O_{14}$ Molecular Weight: 780.95

SUPPORTING DOCUMENTS:

NDA 9-330 LANOXIN Injection
NDA 18-118 LANOXICAPS

RELATED DOCUMENTS (if applicable): Not applicable.

CONSULTS: None.

REMARKS/COMMENTS:

EER was requested on 11/16/93. No response as yet (8/23/94).

Expiration date - 36 months in HDPE containers and blister packs.

Method validation was done by DDA only. Acceptable for quality control and regulatory purposes.

CONCLUSIONS & RECOMMENDATIONS:

Response to deficiency letter was acceptable.

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig. NDA 20-405
HFD-110/Division File
HFD-110/CunninghamD/8/23/94
HFD-100/CSO
District
HFD-102/CKumkumian [#1 only]
R/D Init by: SUPERVISOR

Danute B. Cunningham

Danute G. Cunningham, Review Chemist
filename: 20405R02.NDA

8/24/94

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-405 **CHEM. REVIEW #:** 3 **REVIEW DATE:** 06-Feb-95

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	30-Sep-93	30-Sep-93	04-Oct-93
AMENDMENTS	27-Jan-95	01-Feb-95	02-Feb-95

NAME & ADDRESS OF APPLICANT: BURROUGHS WELLCOME CO.
3030 Cornwallis Road
Research Triangle Park, NC 27709

Contact person (CMC section): Mr. Wayne Talton
Drug Regulatory Affairs
919-248-8548

DRUG PRODUCT NAME

Proprietary: LANOXIN Tablets
Nonproprietary/USAN: Digoxin
Code Name/#: CAS - 20830-75-5
Alternate names: 38U
38U57
Rougoxin
Chloroformic Digitalin
Homolle's Digitalin
Digacin
Lanicor
12β-Hydroxydigitoxin
Cordioxil
Davoxin
Dixina
Lanocardin
Dilanacin

Chem.Type/Ther.Class: 3 S, 7 S

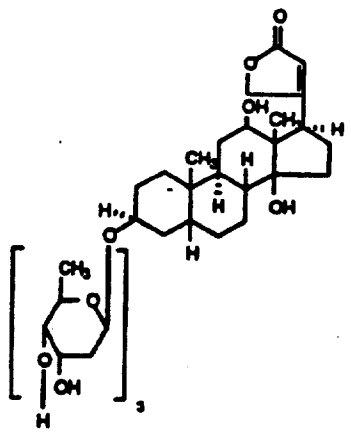
ANDA Suitability Petition/DESI/Patent Status:

Three (3) year marketing exclusivity for Lanoxin (digoxin) Tablets is requested.

PHARMACOL.CATEGORY/INDICATION: Treatment of heart failure in patients receiving angiotensin converting enzyme (ACE) inhibitors and diuretics or diuretics alone.

DOSAGE FORM: Tablets
STRENGTHS: 62.5, 125, 187.5, 250, 375, and 500 μg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: X Rx _____ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Chemical name(s):

3β-[(*O*-2,6-Dideoxy-β-*D*-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β-card-20(22)-enolide (IUPAC)

(3β,5β,12β)-3-[(*O*-2,6-Dideoxy-β-*D*-*ribo*-hexapyranosyl-(1→4)-*O*-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl)oxy]-12,14-dihydroxycard-20(22)-enolide (Chem. Abstr.)

Molecular Formula: $C_{41}H_{64}O_{14}$ Molecular Weight: 780.95

SUPPORTING DOCUMENTS:

NDA 9-330 LANOXIN Injection
NDA 18-118 LANOXICAPS

RELATED DOCUMENTS (if applicable): Not applicable.

CONSULTS: None.

REMARKS/COMMENTS:

Expiration date - 36 months in HDPE containers and blister packs.

Method validation was done by DDA only. Acceptable for quality control and regulatory purposes.

CONCLUSIONS & RECOMMENDATIONS:

Response to deficiency letter was acceptable.

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig. NDA 20-405
HFD-110/Division File
HFD-110/CunninghamD/2/6/95
~~HFD-100/CSO~~
District
HFD-102/CKumkumian [#1 only]
R/D Init by: SUPERVISOR

Danute G. Cunningham

Danute G. Cunningham, Review Chemist
filename: 20405R03.NDA

2-6-95

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-405 **CHEM. REVIEW #:** 4 **REVIEW DATE:** 13-Dec-95

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	30-Sep-93	30-Sep-93	04-Oct-93
AMENDMENTS	01-Dec-95	04-Dec-95	08-Dec-95

NAME & ADDRESS OF APPLICANT: BURROUGHS WELLCOME CO.
3030 Cornwallis Road
Research Triangle Park, NC 27709

12/1/95 amendment: Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 17709

Contact person (CMC section): Mr. Wayne Talton
Drug Regulatory Affairs
919-248-8548

12/1/95 amendment: Elizabeth A. Nies
Associate Director
Regulatory Affairs
919-315-8499

DRUG PRODUCT NAME

Proprietary: LANOXIN Tablets
Nonproprietary/USAN: Digoxin
Code Name/#: CAS - 20830-75-5
Alternate names: 38U
38U57
Rougoxin
Chloroformic Digitalin
Homolle's Digitalin
Digacin
Lanicor
12β-Hydroxydigitoxin
Cordioxil
Davoxin
Dixina
Lanocardin
Dilanacin
Chem.Type/Ther.Class: 3 S, 7 S

ANDA Suitability Petition/DESI/Patent Status:

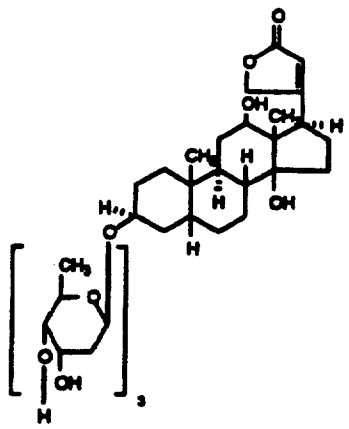
Three (3) year marketing exclusivity for Lanoxin (digoxin) Tablets is requested.

PHARMACOL.CATEGORY/INDICATION: Treatment of heart failure in patients receiving angiotensin converting enzyme (ACE) inhibitors and diuretics or diuretics alone.

12/1/95: Treatment of Congestive Heart Failure

DOSAGE FORM: Tablets
STRENGTHS: 62.5, 125, 187.5, 250, 375, and 500 μg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: __X__ Rx _____ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Chemical name(s):

3β-[(*O*-2,6-Dideoxy-β-*D*-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β-card-20(22)-enolide (IUPAC)

(3β,5β,12β)-3-[(*O*-2,6-Dideoxy-β-*D*-*ribo*-hexapyranosyl-(1→4)-*O*-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl)oxy]-12,14-dihydroxycard-20(22)-enolide (Chem. Abstr.)

Molecular Formula: $C_{41}H_{64}O_{14}$ Molecular Weight: 780.95

SUPPORTING DOCUMENTS:

NDA 9-330 LANOXIN Injection
NDA 18-118 LANOXICAPS

RELATED DOCUMENTS (if applicable): Not applicable.

CONSULTS: None.

REMARKS/COMMENTS:

Expiration date - 36 months in HDPE containers and blister packs.

Method validation was done by DDA only. Acceptable for quality control and regulatory purposes.

APPEARS THIS WAY
ON ORIGINAL

CONCLUSIONS & RECOMMENDATIONS:

Responses to deficiency letter were acceptable.

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig. NDA 20-405
HFD-110/Division File
HFD-110/CunninghamD/12/13/95
HFD-100/CSO
District

R/D Init by: SUPERVISOR

Danute G. Cunningham, Review Chemist
filename: 20405R04.NDA

12/14/95

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

OCT 8 1996

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-405 **CHEM. REVIEW #:** 5 **REVIEW DATE:** 08-Oct-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	30-Sep-93	30-Sep-93	04-Oct-93
AMENDMENTS	26-Sep-96	27-Sep-96	01-Oct-96

NAME & ADDRESS OF APPLICANT:

BURROUGHS WELLCOME CO.
3030 Cornwallis Road
Research Triangle Park, NC 27709

12/1/95 amendment

Glaxo Wellcome Inc. (New applicant)
Five Moore Drive
Research Triangle Park, NC 17709

12/1/95 amendment

Elizabeth A. Nies
Associate Director
Regulatory Affairs
919-315-8499

DRUG PRODUCT NAME

Proprietary: LANOXIN Tablets
Nonproprietary/USAN: Digoxin
Code Name/#: CAS - 20830-75-5
Alternate names: 38U
38U57
Rougoxin
Chloroformic Digitalin
Homolle's Digitalin
Digacin
Lanicor
12β-Hydroxydigitoxin
Cordioxil
Davoxin
Dixina
Lanocardin
Dilanacin

Chem.Type/Ther.Class: 3 S, 7 S

ANDA Suitability Petition/DESI/Patent Status:

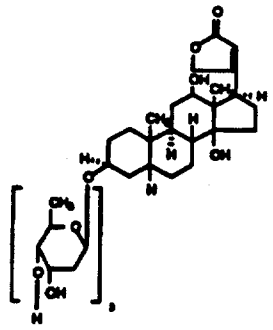
Three (3) year marketing exclusivity for Lanoxin (digoxin) Tablets is requested.

PHARMACOL.CATEGORY/INDICATION: Treatment of heart failure in patients receiving angiotensin converting enzyme (ACE) inhibitors and diuretics or diuretics alone.

12/1/95 Treatment of Congestive Heart Failure

DOSAGE FORM: Tablets
STRENGTHS: 62.5, 125, 187.5, 250, 375, and 500 μg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: __X__ Rx _____ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Chemical name(s):

3β-[(*O*-2,6-Dideoxy-β-*D*-*ribo*-hexopyranosyl-(1-4)-*O*-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl-(1-4)-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β-card-20(22)-enolide (IUPAC)

(3β,5β,12β)-3-[(*O*-2,6-Dideoxy-β-*D*-*ribo*-hexapyranosyl-(1-4)-*O*-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl-(1-4)-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl)oxy]-12,14-dihydroxycard-20(22)-enolide (Chem. Abstr.)

Molecular Formula: $C_{41}H_{64}O_{14}$ Molecular Weight: 780.95

SUPPORTING DOCUMENTS:

NDA 9-330 LANOXIN Injection
NDA 18-118 LANOXICAPS

RELATED DOCUMENTS (if applicable): Not applicable.

CONSULTS: None.

REMARKS/COMMENTS:

Expiration date - 36 months in HDPE containers and blister packs.

Method validation was done by DDA only. Acceptable for quality control and regulatory purposes.

Dissolution has been set at Q = at 60 min. Data supporting the dissolution is included. Particle size of digoxin drug substance is directly correlated to tablet dissolution.

CONCLUSIONS & RECOMMENDATIONS:

In the original NDA, the average quantity of digoxin dissolved in 60 min is nlt of labeled strength (tolerance).

The applicant argues that if a Q value of was chosen, then for level 3, 2 tablets could have a dissolution as low as . Since the lowest value obtained since 1991 was , level 3 testing would permit tablets with dissolution values for which no clinical data exists.

The counter argument is that since digoxin has a long half life, an occasional low dissolving tablet would not have an observable clinical effect.

A decision regarding Glaxo's proposal should be made in consultation with the medical officer and biopharm.

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig. NDA 20-405
HFD-110/Division File
HFD-110/CunninghamD/10/3/96
HFD-100/CSO
District
HFD-110/Biopharm reviewer
R/D Init by: SUPERVISOR

Danute G. Cunningham, Review Chemist
filename: 20405R05.NDA

10/8/96

APPEARS THIS WAY
ON ORIGINAL

APR 2 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-405 **CHEM. REVIEW #:** 6 **REVIEW DATE:** 02-Apr-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	30-Sep-93	30-Sep-93	04-Oct-93
AMENDMENT (BZ)	20-Mar-97	24-Mar-97	27-Mar-97

NAME & ADDRESS OF APPLICANT:

BURROUGHS WELLCOME CO.
3030 Cornwallis Road
Research Triangle Park, NC 27709

12/1/95 amendment

Glaxo Wellcome Inc. (New applicant)
Five Moore Drive
Research Triangle Park, NC 17709

12/1/95 amendment

Elizabeth A. Nies
Associate Director
Regulatory Affairs
919-315-8499

DRUG PRODUCT NAME

Proprietary: LANOXIN Tablets
Nonproprietary/USAN: Digoxin
Code Name/#: CAS - 20830-75-5
Alternate names: 38U
38U57
Rougoxin
Chloroformic Digitalin
Homolle's Digitalin
Digacin
Lanicor
12β-Hydroxydigitoxin
Cordioxil
Davoxin
Dixina
Lanocardin
Dilanacin
Chem.Type/Ther.Class: 3 S, 7 S

ANDA Suitability Petition/DESI/Patent Status:

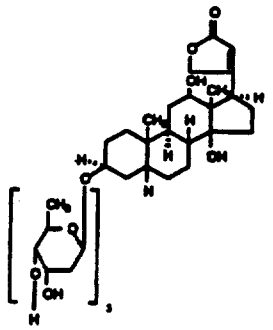
Three (3) year marketing exclusivity for Lanoxin (digoxin) Tablets is requested.

PHARMACOL.CATEGORY/INDICATION: Treatment of heart failure in patients receiving angiotensin converting enzyme (ACE) inhibitors and diuretics or diuretics alone.

12/1/95 Treatment of Congestive Heart Failure

DOSAGE FORM: Tablets
STRENGTHS: 62.5, 125, 187.5, 250, 375, and 500 μg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: __X__ Rx _____ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Chemical name(s):

3β-[(*O*-2,6-Dideoxy-β-*D*-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β-card-20(22)-enolide (IUPAC)

(3β,5β,12β)-3-[(*O*-2,6-Dideoxy-β-*D*-*ribo*-hexapyranosyl-(1→4)-*O*-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl)oxy]-12,14-dihydroxycard-20(22)-enolide (Chem. Abstr.)

Molecular Formula: $C_{41}H_{64}O_{14}$ Molecular Weight: 780.95

SUPPORTING DOCUMENTS:

NDA 9-330 LANOXIN Injection
NDA 18-118 LANOXICAPS

RELATED DOCUMENTS (if applicable): Not applicable.

CONSULTS: None.

REMARKS/COMMENTS:

Expiration date - 36 months in HDPE containers and blister packs.

Method validation was done by DDA only. Acceptable for quality control and regulatory purposes.

Dissolution has been set at Q = · at 60 min. Data supporting the dissolution is included. Particle size of digoxin drug substance is directly correlated to tablet dissolution.

3/20/97 amendment - requests clarification on dissolution specification.

CONCLUSIONS & RECOMMENDATIONS:

Biopharmaceutics will make the final decision.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig. NDA 20-405
HFD-110/Division File
HFD-110/CunninghamD/4/2/97
HFD-100/CSO
District
HFD-110/Biopharm reviewer
R/D Init by: Team Leader

Danute G. Cunningham, Review Chemist
filename: 20405R06.NDA

4/2/97

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY

MAY 20 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-405 **CHEM. REVIEW #:** 7 **REVIEW DATE:** 15-May-97
19-May-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	30-Sep-93	30-Sep-93	04-Oct-93
AMENDMENT (BC)	30-Apr-97	01-May-97	05-May-97

NAME & ADDRESS OF APPLICANT: Glaxo Wellcome Inc. (New applicant)
Five Moore Drive
Research Triangle Park, NC 17709

12/1/95 amendment Elizabeth A. Nies
Associate Director
Regulatory Affairs
919-315-8499

DRUG PRODUCT NAME

Proprietary: LANOXIN Tablets
Nonproprietary/USAN: Digoxin
Code Name/#: CAS - 20830-75-5
Alternate names: 38U
38U57
Rougoxin
Chloroformic Digitalin
Homolle's Digitalin
Digacin
Lanicor
12β-Hydroxydigitoxin
Cordioxil
Davoxin
Dixina
Lanocardin
Dilanacin
Chem.Type/Ther.Class: 3 S, 7 S

ANDA Suitability Petition/DESI/Patent Status:

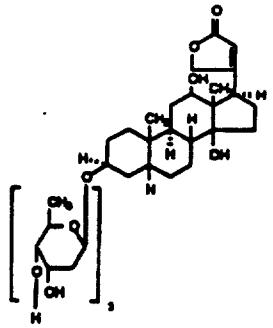
Three (3) year marketing exclusivity for Lanoxin (digoxin) Tablets is requested.

PHARMACOL.CATEGORY/INDICATION: Treatment of heart failure in patients receiving angiotensin converting enzyme (ACE) inhibitors and diuretics or diuretics alone.

12/1/95 Treatment of Congestive Heart Failure

DOSAGE FORM: Tablets
STRENGTHS: 62.5, 125, 187.5, 250, 375, and 500 μg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: __X__ Rx _____ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Chemical name(s):

3β-[(*O*-2,6-Dideoxy-β-*D*-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β-card-20(22)-enolide (IUPAC)

(3β,5β,12β)-3-[(*O*-2,6-Dideoxy-β-*D*-*ribo*-hexapyranosyl-(1→4)-*O*-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl)oxy]-12,14-dihydroxycard-20(22)-enolide (Chem. Abstr.)

Molecular Formula: $C_{41}H_{64}O_{14}$ Molecular Weight: 780.95

SUPPORTING DOCUMENTS:

NDA 9-330 LANOXIN Injection
NDA 18-118 LANOXICAPS

RELATED DOCUMENTS (if applicable): Not applicable.

CONSULTS: None.

REMARKS/COMMENTS:

Expiration date - 36 months in HDPE containers and blister packs.

Method validation was done by DDA only. Acceptable for quality control and regulatory purposes.

Dissolution: Six Tablet Test: Q = at 60 minutes and the quantity of digoxin tablet dissolved in 60 minutes from each tablet must not be less than of the labeled strength at level 1. Twelve Tablet Test: The average quantity of digoxin dissolved in 60 minutes is nlt of labeled strength and the quantity of digoxin dissolved in 60 minutes from each tablet is nlt of labeled strength at level 2.

4/30/97 amendment - updates the regulatory specification for the LANOXIN tablets by including revised dissolution specifications. Alternate manufacturing and packaging site Glaxo Wellcome, Zebulon, NC. Withdrew the Kirkland facility in Quebec, Canada as manufacturing site.

FUR requested on 5/13/97.

CONCLUSIONS & RECOMMENDATIONS:

Glaxo Wellcome adequately presented data to demonstrate that the tablets manufactured at Zebulon are equivalent insofar as the manufacture and stability of the tablets are concerned.

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig. NDA 20-405
HFD-110/Division File
HFD-110/CunninghamD/5/15/97
HFD-100/CSO
HFD-810/Division Director
District
HFD-110/Biopharm reviewer
R/D Init by: Team Leader

Danute G. Cunningham, Review Chemist
filename: 20405R07.NDA

5/20/97

APPEARS THIS WAY
ON ORIGINAL

JL 10 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-405 **CHEM. REVIEW #:** 8 **REVIEW DATE:** 10-Jul-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	30-Sep-93	30-Sep-93	04-Oct-93
AMENDMENT (BL)	03-Jul-97	07-Jul-97	10-Jul-97

NAME & ADDRESS OF APPLICANT: Glaxo Wellcome Inc. (New applicant)
Five Moore Drive
Research Triangle Park, NC 17709

12/1/95 amendment Elizabeth A. Nies
Director
Regulatory Affairs
919-483-9445

DRUG PRODUCT NAME

Proprietary:	LANOXIN Tablets
Nonproprietary/USAN:	Digoxin
Code Name/#:	CAS - 20830-75-5
Alternate names:	38U 38U57 Rougoxin Chloroformic Digitalin Homolle's Digitalin Digacin Lanicor 12β-Hydroxydigitoxin Cordioxil Davoxin Dixina Lanocardin Dilanacin
Chem.Type/Ther.Class:	3 S, 7 S

ANDA Suitability Petition/DESI/Patent Status:

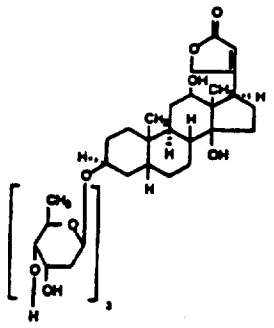
Three (3) year marketing exclusivity for Lanoxin (digoxin) Tablets is requested.

PHARMACOL.CATEGORY/INDICATION: Treatment of heart failure in patients receiving angiotensin converting enzyme (ACE) inhibitors and diuretics or diuretics alone.

12/1/95 Treatment of Congestive Heart Failure

DOSAGE FORM:	Tablets
STRENGTHS:	62.5, 125, 187.5, 250, 375, and 500 μg
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	__X__ Rx _____ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Chemical name(s):

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Molecular Formula: $C_{41}H_{64}O_{14}$ Molecular Weight: 780.95

SUPPORTING DOCUMENTS:

NDA 9-330 LANOXIN Injection
NDA 18-118 LANOXICAPS

RELATED DOCUMENTS (if applicable): Not applicable.

CONSULTS: None.

REMARKS/COMMENTS:

Expiration date - 36 months in HDPE containers and blister packs.

Method validation was done by DDA only. Acceptable for quality control and regulatory purposes.

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7/3/97 amendment - response to approvable letter.

FUR requested on 5/13/97.

CONCLUSIONS & RECOMMENDATIONS:

Proposed changes are to the CLINICAL PHARMACOLOGY and INDICATIONS & USAGE sections only. Labeling is satisfactory for DESCRIPTION and HOW SUPPLIED sections.

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig. NDA 20-405
HFD-110/Division File
HFD-110/CunninghamD/7/10/97
HFD-100/CSO
HFD-810/Division Director
District
HFD-110/Biopharm reviewer
R/D Init by: Team Leader

Danute G. Cunningham, Review Chemist
filename: 20405R08.NDA

7/10/97

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY

SEP 19 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-405 **CHEM. REVIEW #:** 9 **REVIEW DATE:** 18-Sep-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	30-Sep-93	30-Sep-93	04-Oct-93
AMENDMENT (AL)	15-Sep-97	17-Sep-97	18-Sep-97

NAME & ADDRESS OF APPLICANT: Glaxo Wellcome Inc. (New applicant)
Five Moore Drive
Research Triangle Park, NC 17709

12/1/95 amendment

Elizabeth A. Nies
Director
Regulatory Affairs
919-483-9445

DRUG PRODUCT NAME

Proprietary: LANOXIN Tablets
Nonproprietary/USAN: Digoxin
Code Name/#: CAS - 20830-75-5
Alternate names: 38U
38U57
Rougoxin
Chloroformic Digitalin
Homolle's Digitalin
Digacin
Lanicor
12β-Hydroxydigitoxin
Cordioxil
Davoxin
Dixina
Lanocardin
Dilanacin
Chem.Type/Ther.Class: 3 S, 7 S

ANDA Suitability Petition/DESI/Patent Status:

Three (3) year marketing exclusivity for Lanoxin (digoxin) Tablets is requested.

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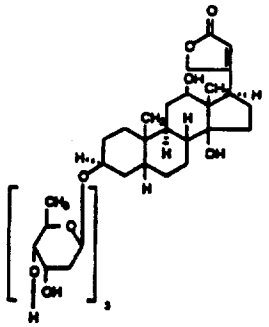
ROUTE OF ADMINISTRATION: Oral
DISPENSED: X Rx _____ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Chemical name(s):

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NDA 18-118 LANOXICAPS

RELATED DOCUMENTS (if applicable): Not applicable.

CONSULTS: None.