

**DigiFab[®], 40mg/vial digoxin immune Fab, powder for solution for infusion
(digoxin immune Fab [ovine])**

PL 21744/0001

UKPAR

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LAY SUMMARY

The MHRA granted Protherics UK Ltd a Marketing Authorisation for the medicinal product DigiFab[®] 40mg/vial digoxin immune Fab, powder for solution for infusion (PL 21744/0001), hereafter referred to as DigiFab, on 1st July 2011. This medicine is subject to restricted medical prescription and is indicated for the treatment of known (or strongly suspected) life-threatening digoxin toxicity associated with ventricular arrhythmias or bradyarrhythmias unresponsive to atropine where measures beyond withdrawal of digoxin and correction of serum electrolyte abnormalities are considered necessary.

DigiFab[®] is a sterile, purified, lyophilized preparation of sheep-derived antibody fragments with a high affinity for digoxin. Fragments are obtained from the blood of healthy sheep immunised with a digoxin analogue, digoxin-dicarboxymethoxylamine (DDMA), that contains the functionally essential cyclopenta-perhydrophenanthrene:lactone ring moiety coupled to keyhole limpet haemocyanin (KLH). The final product is prepared by isolating the immunoglobulin fraction of the sheep serum, digesting it with papain and isolating the digoxin-specific Fab fragments by affinity chromatography. The antibody fragments have a molecular weight of about 46kDa.

DigiFab[®] was submitted as a new active substance under Article 8(3) of Directive 2001/83/EC as amended. DigiFab[®] has not been authorised in any other EU member state nor is it the subject of pending application in another EU Member State. DigiFab[®] has been marketed in the USA since February 2002 and was authorised in Switzerland and Canada in 2010.

A critical review of the clinical, pharmaceutical and non-clinical data presented to the MHRA demonstrated that DigiFab[®] is effective in the treatment of known (or strongly suspected) life-threatening digoxin toxicity associated with ventricular arrhythmias or bradyarrhythmias unresponsive to atropine where measures beyond withdrawal of digoxin and correction of serum electrolyte abnormalities are considered necessary.

DigiFab[®], 40mg/vial digoxin immune Fab, powder for solution for infusion

(digoxin immune Fab [ovine])

PL 21744/0001

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of data on quality, safety and efficacy the UK granted a Marketing Authorisation to Protherics UK Ltd for the medicinal product DigiFab® 40mg/vial digoxin immune Fab, powder for solution for infusion (PL 21744/0001), hereafter referred to as DigiFab® on 1st July 2011. This product is a restricted prescription only medicine.

This application was submitted as a new active substance national application under Article 8(3) of Directive 2001/83/EC as amended.

DigiFab® is a sterile, purified, lyophilised preparation of digoxin-immune ovine Fab (monovalent) immunoglobulin fragments and is indicated for the treatment of known (or strongly suspected) life-threatening digoxin toxicity associated with ventricular arrhythmias or bradyarrhythmias unresponsive to atropine where measures beyond withdrawal of digoxin and correction of serum electrolyte abnormalities are considered necessary.

Each vial of DigiFab®, which will bind approximately 0.5 mg digoxin, contains 40 mg of digoxin immune Fab, 75 mg (approximately) of mannitol, and 2 mg (approximately) sodium acetate as a buffering agent. The product contains no preservatives and is intended for intravenous administration after reconstitution with 4 ml of sterile Water for Injection.

DigiFab® has an affinity for digoxin in the range of 10^9 to 10^{10} M^{-1} , which is greater than the affinity of digoxin for its sodium pump receptor, the presumed receptor for its therapeutic and toxic effects. When administered to the intoxicated patient, digoxin immune Fab binds to molecules of digoxin reducing free digoxin levels, which results in a shift in the equilibrium away from binding to the receptors, thereby reducing cardio-toxic effects. Fab-digoxin complexes are then cleared by the kidney and reticuloendothelial system.

DigiFab® was granted a licence on 1st July 2011.

QUALITY ASSESSMENT

I. INSPECTION STATUS

A product specific inspection has been performed and is satisfactory.

II. INTRODUCTION

Digoxin specific antibody binding fragments [digoxin immune Fab (Ovine)] are derived from antibodies produced in sheep immunised to digoxin. Digoxin has greater affinity for the antibodies than for tissue-binding sites, and the digoxin-antibody complex is then rapidly excreted in the urine. Digoxin-specific antibody fragments are generally restricted to the treatment of life-threatening digoxin or digitoxin intoxication in which conventional treatment is ineffective. Successful treatment of lanatoside C poisoning has also been reported.

It is estimated that 38 mg of antibody fragments could bind about 0.5 mg of digoxin or digitoxin and the dose calculation is based on this estimate and the body-load of digoxin (based on the amount ingested or ideally from the steady-state plasma concentration). Administration is by intravenous infusion over a 30-minute period. In patients considered to be at high risk of an allergic response an intradermal or skin scratch test may be performed (Martindale).

Digoxin Immune Fab is classed as a digitalis antitoxin, ATC code VO3A B24

III. DRUG SUBSTANCE

III.1 General information

The drug substance is defined as the 'formulated bulk solution'. The starting material for manufacture is sheep antisera from Australian flocks and drug substance manufacture includes the stage of manufacture up to the sterile filtration of the formulated bulk solution. Thereafter, filling and lyophilisation of the final bulk formulated solution is defined as drug product manufacture.

III.1.1 Nomenclature

Digoxin Immune Fab (Ovine) – affinity purified digoxin specific Fab fragments of sheep antibodies.

III.1.2 Structure

The primary structure cannot be determined for the multi-component polyclonal Fab.

III.1.3 General properties

Details of biophysical testing for digoxin binding capacity, avidity, iso-electric range, molecular weight, purity, absorptivity and secondary structure have been reported.

III.2 Manufacture

III.2.1 Manufacturers

Details of the drug substance manufacturers and their responsibilities have been provided and are satisfactory.

III.2.2 Description of manufacturing process and process controls

The manufacturing process has been adequately summarised by flow diagram. The overview of the production of ovine anti-digoxin immunoglobulin is acceptable. A detailed description of the process is provided in the dossier and is satisfactory.

III.2.3 Control of materials

Components for the manufacture of bulk product are classified. Compendial materials are adequately tested. This is satisfactory.

III.2.4 Control of critical steps and intermediates

Critical steps have been defined and specifications provided. This is satisfactory.

III.2.5 Process validation

The applicant has provided the summary of validation carried out on the manufacture of drug substance. The consistency of the manufacturing process has been adequately demonstrated for each process step.

III.2.6 Manufacturing process development

An overview of the manufacturing development has been provided and includes results of studies to establish the current process and discussion of changes in the method of manufacture with increasing scale during the development of the product. The manufacturing process development has been adequately described.

III.3 Characterisation

III.3.1 Elucidation of structure and other characteristics

The active ingredients(s) compose multi-component, polyclonal Fab affinity purified from sheep serum.

Biophysical characteristics have been reported in the dossier and are satisfactory.

III.3.2 Impurities

Potential impurities are adequately described and the drug substance specification includes controls for each.

III.4 Control of drug substance

III.4.1 Specification

The drug substance specification is satisfactory.

III.4.2. Analytical procedures

Copies of standard operating procedures have been provided as descriptions of the analytical methods. These are acceptable. Summaries of assays have been provided and are adequate.

III.4.3 Validation of analytical procedures

All methods have been adequately validated and the validation reports provided. This is satisfactory.

III.4.4 Batch analyses

Batch analytical results have been provided for several batches of formulated bulk product. All batches comply with the proposed specifications. The MAH have committed to providing additional prospective batch release testing data with a new assay.

III.4.5. Justification of specification

The specifications have been adequately justified and their methods described. The MAH have committed to a review of the release specification limits for the drug substance once data is available for a predetermined number of additional lots of DigiFab[®]. This is acceptable

III.5 Reference standards or materials

The current working standard is a batch manufactured according to the commercial process. An earlier batch was used in the validation of analytical methods. Results of characterisation studies for the standards have been reported and are satisfactory.

III.6 Container closure system

Storage of the in-process stages and drug substance has been adequately described. The containers are USP and Ph. Eur. compliant for use as parenteral containers. This is acceptable.

III.7 Stability

III.7.1 Stability summary and conclusions

Stability of the drug substance has been demonstrated using several commercial-scale conformance batches. Batches have been assessed for colour, clarity, pH, protein concentration, endotoxin, purity and potency.

III.7.2 Post-approval stability protocol and stability commitment

One batch will be entered into stability studies each year.

III.7.3. Stability data

Tabulated data support the conclusions above.

IV. DRUG PRODUCT

IV.1 Composition of the drug product

Each vial of DigiFab® contains 40 mg of digoxin immune Fab (ovine) protein as a sterile, lyophilized, off-white powder. Each vial of DigiFab® should be reconstituted with 4mL of sterile water for injection. The excipients are sodium acetate, acetic acid and mannitol. The drug product has been adequately described.

IV.2 Pharmaceutical development

The presentation of DigiFab® is a sterile, lyophilised, crystalline, off-white powder containing antigen-binding fragments derived from specific antidigoxin antibodies raised in sheep. A satisfactory account of the pharmaceutical development has been provided.

IV.3 Manufacture

IV.3.1 Manufacturer(s)

Details of the product manufacturer and its responsibility have been provided. Current GMP certificates have been provided and are satisfactory. Details of QC testing and batch release site have also been provided.

IV.3.2 Batch formula

The typical batch size for filling and lyophilisation and the validated batch size range have been provided. The applicant has provided a detailed batch manufacturing formula.

IV.3.2 Description of manufacturing process and process controls

The production steps and in-process controls performed in the manufacture of the drug product are adequately described.

IV.3.3 Process validation and/or evaluation

Analytical methods have been adequately validated and the process has been presented and appropriately described. The MAH has committed to provide further manufacturing process validation as requested. This is acceptable.

IV.4 Control of excipients

Each of the excipients used complies with its respective pharmacopoeial monograph and none of the excipients are of human or animal origin.

IV.5 Control of drug product

IV.5.1 Finished product specification

The finished product specification has been provided. Satisfactory control tests are applied at the time of release.

IV.5.2 Analytical procedures

Copies of standard operating procedures have been provided describing the analytical methods specific to the drug product. This is satisfactory.

IV.5.3 Validation of analytical procedures

Validation data have been supplied and are considered adequate.

IV.5.4 Batch analyses

Analytical results for several batches have been provided and comply with the specification.

IV.5.5 Characterisation of impurities

The applicant has demonstrated that process related impurities are well controlled.

IV.5.6 Justification of specification(s)

The applicant has provided the specifications for DigiFab®. The MAH has committed to a review of the release specification limits for the drug product once data is available for a predetermined number of additional lots of DigiFab®. This is acceptable

IV.6 Reference standards or materials

The history of reference standards has been summarised. Reference standards have been characterised using appropriate immunochemical and physicochemical methods.

IV.7 Container closure system

The container and closure conform to Ph.Eur. and are acceptable.

IV.8 Stability

IV.8.1 Stability summary and conclusion

Real time and accelerated stability studies have been carried out on production scale lots of DigiFab using the same container/closure system as used for batches for commercial sales. A 3 year shelf life has been assigned and is acceptable.

IV.8.2 Post-approval stability protocol and stability commitment

The MAH commits to placing one lot of drug product on real time (long-term) stability monitoring each year of manufacture. In addition, the MAH commits to placing several lots of DigiFab on stability to support potency determination. This is satisfactory.

IV.8.3 Stability data

The MAH has provided tabulated data which support the conclusions above. This is satisfactory.

V. APPENDICES

V.1 Facilities and equipment

Details of product manufacturing facilities and equipment are acceptable.

V.2 Adventitious agents safety evaluation

The risk of adventitious viral contamination has been discussed and is satisfactory.

V.3 Novel excipients

Not applicable.

VI. REGIONAL INFORMATION

Not applicable.

VII. ASSESSOR'S COMMENTS ON THE SPC, LABELS AND PACKAGE LEAFLET

VII.1 Summary of product characteristics

The SPC is satisfactory.

VII.2 Patient information leaflet

The PIL is satisfactory.

VII.3 Labels

The labels are acceptable.

VII.4 MAA form

Acceptable.

VIII.ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

The application is approvable.

PRECLINICAL ASSESSMENT

I. INTRODUCTION

This is a national application for DigiFab[®], a digoxin immune Fab product. The proposed therapeutic indication is (from the SPC): *“for the treatment of known (or strongly suspected) life-threatening digoxin toxicity associated with ventricular arrhythmias or bradyarrhythmias unresponsive to atropine where measures beyond the withdrawal of digoxin and correction of serum electrolyte abnormalities are considered necessary.”*

DigiFab[®] is purified, lyophilised digoxin-immune ovine Fab (monovalent) immunoglobulin fragments, obtained from the blood of healthy sheep immunised with digoxin derivative (digoxin dicarboxymethoxylamine) coupled to keyhole limpet haemocyanin. DigiFab[®] has a higher affinity for digoxin than digoxin has for its pump receptor hence it binds to digoxin molecules reducing digoxin free serum levels and reducing the cardiotoxic effect.

The original application for DigiFab[®] was submitted in 2004 as a national abridged application, with the applicant claiming that DigiFab[®] was essentially similar to Digibind Injection. Following a meeting with the MHRA in December 2005, the applicant has resubmitted the dossier as a stand alone application.

The applicant was advised that if the product were to be considered as a new application non-clinical data would be required.

II. NON-CLINICAL ASPECTS

DigiFab[®] is a digoxin-immune ovine Fab fragment antidote for the treatment of digoxin toxicity. The applicant states that it is similar in character and method of manufacture to Digibind (GlaxoSmithKline). The applicant states that their non-clinical programme was limited to studies designed to demonstrate comparability between DigiFab[®] and Digibind with regard to their ability to bind to digoxin and digoxin-like analogues and efficacy in vivo.

II.1 Pharmacodynamics

No studies have been conducted. The applicant's stated rationale for not presenting non-clinical studies is based on the premise that DigiFab[®] is the same as Digibind in its pharmacological behaviour. DigiFab[®] and Digibind are both ovine immune Fab products designed to bind and neutralise digoxin and its analogues in order to reduce their toxic effects. The mechanism of action is based on the fact that these products bind digoxin with a higher affinity than its sodium pump receptor therefore causing redistribution of digoxin away from tissues.

II.2 Pharmacokinetics

Conventional pharmacokinetic studies were not conducted with DigiFab[®] because of the availability of human and non-clinical information in the published literature.

II.3 Toxicology

The applicant states that toxicology studies of heterologous products have not been required historically on the basis that they are not intended for long term use, there is a long history of use of animal-derived antisera products such that their potential side effects are well known and defined, and these products are natural proteins as opposed to manufactured or engineered proteins. Specifically, toxicity studies were not conducted due to the well-documented safety of Digibind and other affinity purified Fab immunotherapies used clinically at similar dose levels, together with the studies with DigiFab[®] in human volunteers and patients submitted in this application.

In summary, the applicant has not submitted any new non-clinical studies. The non-clinical information consists of a selected review of the literature.
The applicant has provided a written summary of this information which is considered adequate.

IV. Assessor's conclusion

The non-clinical testing strategy for DigiFab[®] was based on the premise that DigiFab[®] is the same as Digibind in its pharmacological behaviour. It appears reasonable to assume that since DigiFab[®] and Digibind are both ovine immune Fab products designed to bind and neutralise digoxin and its analogues in order to reduce their toxic effects their mechanism of action will be similar. The mechanism of action is based on the fact that these products bind digoxin with a higher affinity than its sodium pump receptor, therefore causing redistribution of digoxin away from tissues.

In view of the information available from the published literature further non-clinical studies may not be required, rather conclusions concerning the efficacy or safety of DigiFab[®] should be gained from the clinical data.

Section 5.3 of the SPC (Preclinical safety data) is acceptable.
There are no major non-clinical issues. This application can be approved.

CLINICAL ASSESSMENT REPORT

I. INTRODUCTION

I.1 Studies submitted by the applicant

(Please note that at the time of these trials DigiFab was referred to as a previous name, DigiTAb).

The applicant has submitted 3 studies to support the current application:

A. Study Tab007-02: an open-label, parallel, pharmacokinetic and pharmacodynamic comparison between DigiTAb and Digibind.

B. Study TAb007-01: a trial to determine the safety, pharmacokinetics and pharmacodynamics of affinity purified, Digoxin Immune Fab, Ovine.

C. Study PR007-CLN-rpt003: multicenter retrospective review of the clinical efficacy and safety of DigiFab® in Digoxin poisoned patients.

Studies Tab007-02 and TAb007-01 were presented to the Commission on Human Medicines for consideration in July 2007: these studies were assessed for equivalence between the current product and Digibind (originator). The applicant has since been advised to re-assign the current product as a new active substance on the grounds that the applicant was unable to demonstrate adequate similarity to the originator product: on this basis, this document contains a re-assessment of these studies.

Study PR007-CLN-rpt003, a retrospective study on the use of the current product in the USA where the current product has market authorisation, was submitted by the applicant after July 2007 and following discussion with MHRA.

Each study is described in turn:

I.1.1 Study Tab007-02

Study title: An open-label, parallel, pharmacokinetic and pharmacodynamic comparison between DigiTAB and Digibind

Study number: Tab007-02

GCP certification

The applicant states that the study “was performed in compliance with Good Clinical Practice”. The sponsor provided a monitor to ensure compliance.

Ethical approval

The applicant states that the study was performed in accord with the Declaration of Helsinki, as described, and that the study was approved by local Institutional Review Boards. The applicant states that subjects were volunteers and signed a consent form.

Objectives:

Overall trial objective:

- to compare the pharmacokinetic and pharmacodynamic response of DigiTAB and Digibind given to healthy volunteers two hours after they had received an intravenous digoxin dose.

Primary objective:

- to show that DigiTAB and Digibind have comparable bioaffinity (in vivo binding) by assessing the area under the free digoxin curve from 2 hours (start of the DigiTAB / Digibind infusion) to the last measurement at 48 hours.

Secondary objectives:

- to assess pharmacokinetic parameters (AUC, systemic clearance, maximum serum concentrations and time to maximum serum concentrations) for total digoxin and ovine Fab.
- to compare the pharmacodynamic response to DigiTAB and Digibind as assessed by serial ECG analysis.

Clinical assessor comment: objectives were to compare DigiTAB and Digibind on the basis that the original application was as a generic medicinal product for Digibind. The applicant has been advised to revise the route of application and to claim the current product as a new clinical entity. This assessment will therefore be orientated towards the current product.

Inclusion criteria

Volunteer subjects were eligible for enrolment in this study, if they were:

- healthy, based on a physical examination, medical history, clinical laboratories, ECG and vital signs at the screening visit
- between 21 and 35 years of age
- of body weights falling within -15% to + 25% of ideal body weight
- able to communicate effectively with the study personnel
- properly informed of the nature and risks of the study and gave informed consent in writing and were able to participate for the full term of the trial.

Exclusion criteria

To include only healthy volunteers, any of the following conditions were cause for exclusion from the study:

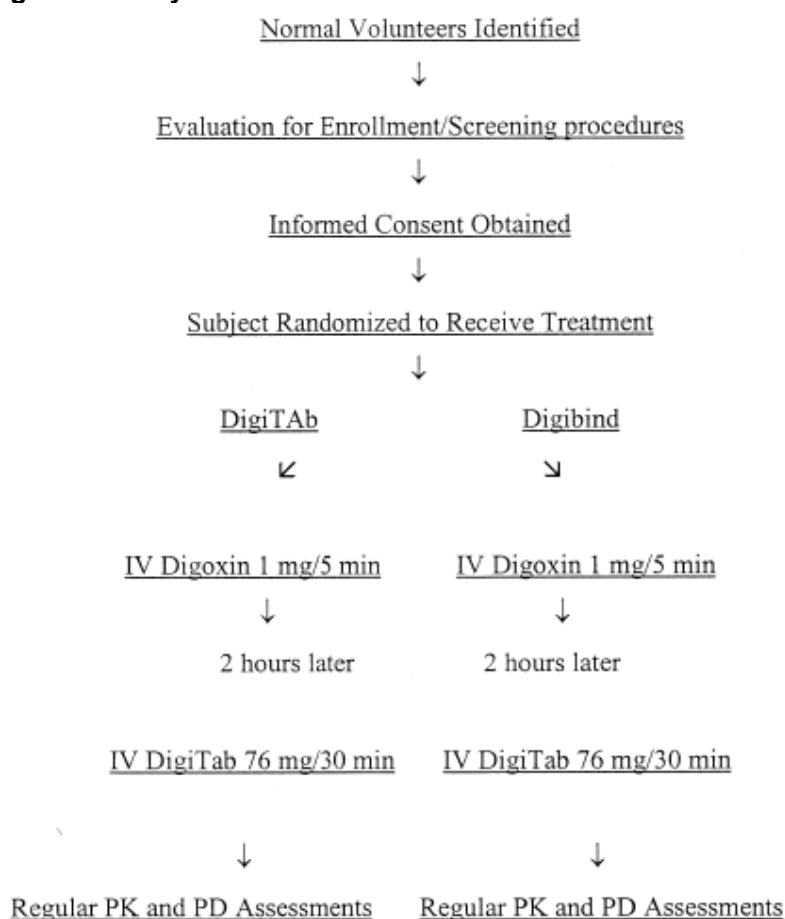
- clinically significant history of cardiac, pulmonary, hepatic, or renal diseases
- current intake or plan to take any prescription (with the exception of oral contraceptives and antibiotics), illicit or experimental drugs or intake of an experimental medication within four weeks prior to entering the study

- inability to give informed consent
- had earlier been given digoxin immune Fab or had known history of hypersensitivity to sheep-derived products
- history of asthma or allergies to antibiotics
- pregnancy or possibility to become pregnant during the study period
- known to be HIV positive
- smoking tobacco products or have a positive cotinine test at anytime during the screening period
- and positive results in intracutaneous or conjunctival allergy test.

Clinical assessor comment: inclusion/exclusion criteria are acceptable.
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Study flow is shown in the following diagram:

Figure 1. Study schematic



Study design: open label, parallel design (chosen because of concerns of carry-over and development of antibodies to test product). Laboratory measurements were carried out blinded.

Number of subjects studied

16 subjects enrolled and 16 subjects were analysed and included in the statistical analysis. There were 8 men and 8 women aged 22–33yrs. All completed the study. Full demographic data are supplied in appendix 16.2.4 of the submitted study report and the following table:

Table 1. Demographic data

Demographic Parameters	Total Volunteers n=16	DigiTAb Group n=8	Digibind Group n=8
Mean age (\pm SD)	27 (3)	29 (4)	26 (2)
range	22 - 33	22 - 33	24 - 30
Mean body weight, kg (\pm SD)	73 (8)	74 (9)	72 (7)
Mean height, cm (\pm SD)	177 (7)	180 (7)	174 (6)
Frame size			
Small	2	0	2
Medium	12	6	6
Large	2	2	0
Gender			
Male	8	4	4
Female	8	4	4
Race			
Caucasian	16	8	8
Hispanic	0	0	0
Asian	0	0	0
Native American	0	0	0

Subjects were randomised in blocks of 4: the randomisation sequence is given in appendix 16.1.7 of the submitted study report.

Clinical assessor comment: The randomisation scheme appears random.

Protocol

Subjects in both treatment groups received 1 mg of digoxin in 8 mL of sterile water infused through a peripheral intravenous catheter over 5 minutes using a syringe driver pump. The digoxin infusion was administered during the protocol time -5 min to 0 hours.

Two hours after the end of the digoxin infusion, eight volunteers received either 76 mg of Digibind or DigiTAb in 200 mL of normal saline infused intravenously over 30 minutes using a peristaltic pump. Two hours was chosen as the starting time as a compromise between tissue distribution and renal elimination of digoxin.

Blood samples for digoxin and Fab analysis were taken immediately before infusion of digoxin, upon completion of the digoxin infusion (time zero) and at 30 minutes, 1, 2, 2.5, 3, 4, 6, 8, 12, 24 and 48 hours after the digoxin infusion.

Urine was collected 24 hours prior to digoxin dosing to determine creatinine clearance and as baseline measurement of digoxin and Fab. Urine was then collected during the intervals 0–4, 4–8, 8–12 and 12–24 hours for determination free and total digoxin and Fab.

Digoxin (total and free) and Fab were measured using immunoassays: for details of assays, refer to accompanying Quality Assessment Report.

Pharmacokinetic statistical analysis of results was carried out using Microsoft Excel ver 8 and WinNonlin. The applicant reports C_{max} , AUC, Vss, Clearance, half-life and other parameters, as described.

Protocol deviations

Protocol deviations are shown in appendix 16.2.2: all deviations were considered by the applicant to be minor and not affect the outcome of the study.

Clinical assessor comment: 6 deviations are reported and concern timings, concomitant medication and smoking status: it is acknowledged that reported deviations most likely did not

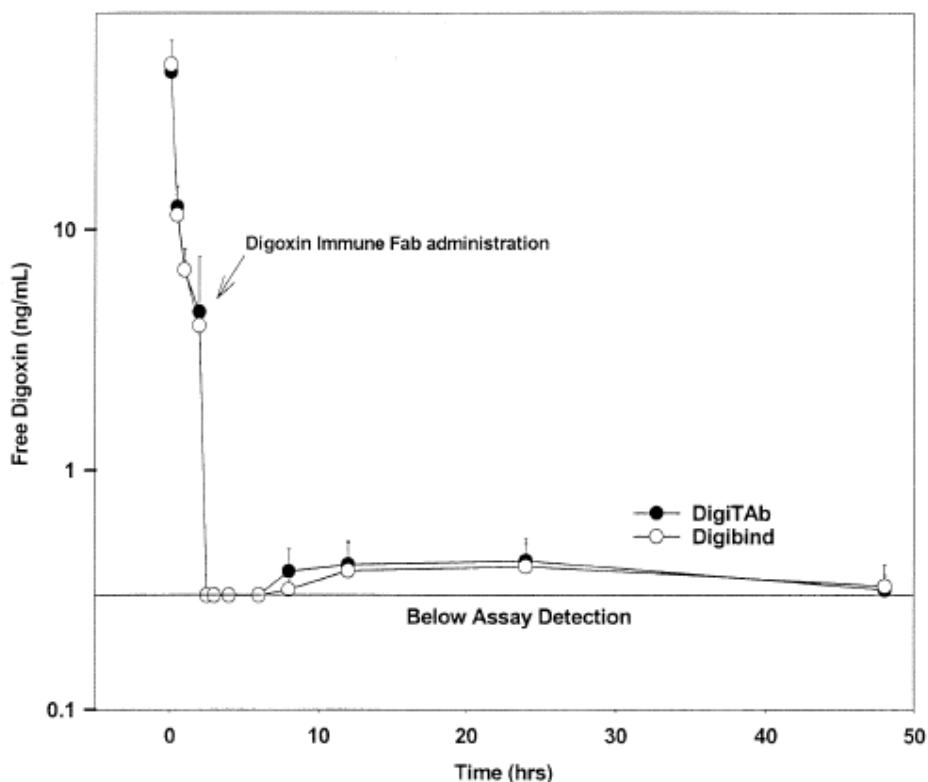
affect overall outcome of study.

Efficacy

Primary outcome: free digoxin concentration in serum

Figure 2. Serum Concentration versus Time for Free Digoxin.

This graph illustrates concentrations of free digoxin (ng/mL) in serum during 48 hours after digoxin administration (1 mg at time zero). At 2 hours, 76 mg of either DigiTab or Digibind was administered over 30 minutes. The assay limit of quantitation is 0.3 ng/mL, and concentrations are shown as mean values with error bars representing standard deviations.

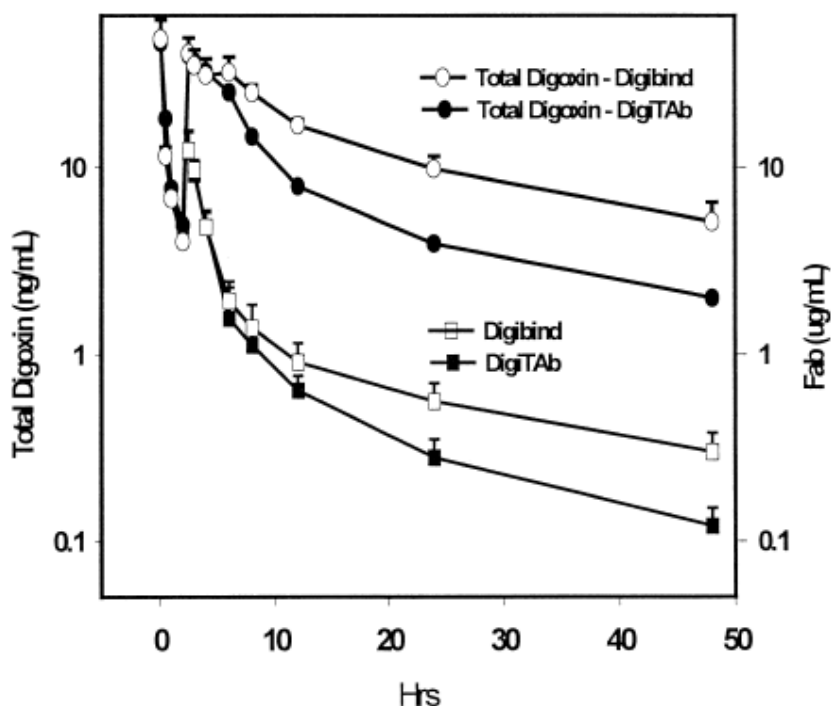


Clinical assessor comment: the above graph does not display free digoxin in the presence of DigiTab between 0hr and 8hrs (1st plot is at 8hrs) because the analyte was below the detection limit. The applicant acknowledges that attempts to compute AUC for free digoxin lack meaning. It is confirmed that DigiTab presence lowers free digoxin concentration, as described. The results of the applicant suggest that the current product is similar to the current UK market leader, Digibind, with regards to effect on free digoxin concentration in healthy volunteers.

Total digoxin assay:

Figure 3. Serum Concentration Versus Time for Total Digoxin and Ovine Fab.

This graph shows concentrations of total digoxin (ng/mL) and Fab (µg/mL) in serum during the 48-hour sampling period following digoxin dosing (1 mg). At 2 hours, 76 mg of either DigiTab or Digibind was administered over 30 minutes. The assay limit of quantitation is 1.5 ng/mL for total digoxin and 0.055 µg/mL for ovine Fab. Concentrations are shown as mean values with error bars representing standard deviations.



Clinical assessor comment: the presence of high concentrations of total digoxin give reassurance that the free digoxin results are credible (and do not reflect absence of digoxin). The half-life of total digoxin in the DigiTab group is reported as 18.1hrs and is somewhat lower than that reported for digoxin in absence of Fab (ie 20–50hrs): this presumably reflects the different kinetics of the antigen-antibody complex.

The applicant reports that (about) 43% of digoxin was excreted in the urine by 24hrs compared to (about) 4% of DigiTab.

Secondary objectives: pharmacokinetic parameters for DigiTab:

The following results are presented:

Table 2. Serum DigiFab® pharmacokinetic parameters

Subject	AUC _{2-∞} (µg/ml*hr)	Cl _{total} (ml/min)	t _{1/2α} (hr)	t _{1/2β} (hr)	Vc (L/kg)	C _{max} (µg/ml)
DigiFab group						
1	32.0	39.6	1.4	24.1	0.13	7.1
4	31.8	39.9	0.7	13.2	0.06	11.2
6	39.5	32.1	0.7	13.4	0.05	13.3
7	32.8	38.7	0.8	12.4	0.06	10.4
9	51.8	24.5	1.2	15.4	0.07	13.4
12	44.2	28.6	1.1	13.5	0.08	14.6
15	46.5	27.2	1.1	14.7	0.07	14.5
16	49.3	25.7	1.2	16.6	0.08	15.3
Mean	41.0	32.0	1.0	15.4	0.08	12.5
SD	8.1	6.5	0.3	3.8	0.02	2.8

Clinical assessor comment: the applicant reports that the half-life of the current product is (about) 15hrs: the applicant acknowledges that the terminal elimination rate was calculated from the last 2 or 3 measurements per subject thereby limiting the accuracy of the estimated half-life. Nonetheless, there is reassurance as much as in the comparator arm of the current study, the applicant reports a half-life for Digibind (GSK, originator) of (about) 23hrs (as shown in the table below) whilst the SPC/PIL for Digibind reports the half-life of Digibind as 16 to 20hrs.

Serum Digibind pharmacokinetic parameters

Subject	AUC _{2-∞} (µg/ml*hr)	Cl _{total} (ml/min)	t _{1/2α} (hr)	t _{1/2β} (hr)	Vc (L/kg)	C _{max} (µg/ml)
Digibind group						
2	61.3	20.7	1.2	30.2	0.07	11.3
3	53.4	23.7	0.9	33.0	0.06	15.3
5	50.1	25.3	0.8	22.3	0.09	9.6
8	73.7	17.2	1.2	24.4	0.07	13.3
10	42.8	29.6	0.7	15.1	0.06	13.2
11	60.4	21.0	1.1	17.9	0.08	13.0
13	76.1	16.7	1.0	23.6	0.07	14.0
14	66.5	19.0	0.9	19.4	0.07	14.6
Mean	60.5	21.6	1.0	23.2	0.07	13.0
SD	11.5	4.4	0.2	6.1	0.01	1.8

Subject	AUC _{2-∞} (µg/ml*hr)	Cl _{total} (ml/min)	t _{1/2α} (hr)	t _{1/2β} (hr)	Vc (L/kg)	C _{max} (µg/ml)
p-value	0.002	0.002	0.6	0.008	0.7	0.6

AUC = area under the DigiFab or Digibind concentration-time curve

Cl = clearance

t_{1/2} = half-life

C_{max} = maximum DigiFab or Digibind concentration

NS = not significant

Measurements of C_{max}, AUC and clearance are noted. The applicant reports that it was not

possible to record the steady state volume of distribution because of incomplete results. The applicant has not provided convincing data to support estimation of V_c .

It has previously been considered that the significant statistical differences in clearance and half-life mitigate against claims for similarity between the current product and Digibind (GSK, market leader).

The half-life of (about) 15hrs for DigiFab® would suggest that, in the clinical setting and after administration of DigiFab, then assay for total serum digoxin would report spurious results for up to 75hrs (i.e. up to 5 half-lives of the current product).

With regard to the reported pharmacokinetic data for DigiFab®, reference is made to: CHMP/EWP/89249/2004 Jan 2007 Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins refers to: absorption, disposition, multiple dosing, variability, special populations and immunogenicity. Each subject is referred to below, wording from the guideline is shown in *italics*:

Absorption: not applicable for the intravenous route

Disposition: *The main elimination pathway should be identified. However, for therapeutic proteins this could be predicted, to a large extent, from the molecular size and specific studies may not be necessary. Catabolism of proteins occurs, usually, by proteolysis. Small proteins of MW < 50,000 Da are eliminated through renal filtration (renal filtration becomes increasingly important the lower the molecular weight) followed by tubular re-absorption and subsequent metabolic catabolism.*

Clinical assessor comment on disposition: the current product may be regarded as a 'small protein'. The applicant has submitted non-clinical data to confirm that the current product is eliminated/metabolised by the kidney. Formal clinical studies to confirm the route of elimination may not be required. The applicant has submitted data that indicate that the half-life of the current product is (about) 15hrs in healthy volunteers.

There is an inverse correlation between steady state volume of distribution (V_{ss}) and molecular weight. A comparable relationship is seen also for permeability and molecular weight.

Clinical assessor comment: the steady state volume of distribution, though of interest, may be regarded as a secondary consideration to the ability of the current product to lower the concentration of free digoxin in plasma.

Multiple-dosing: not applicable to the current product

The inter-subject variability should be estimated and if possible the important sources of the variability e.g. demographic factors as weight and age, should be identified. Based on the results individualised dosing should be considered if necessary from safety and efficacy perspectives. The variability within an individual should be quantified for products intended for multiple-dose administration.

Clinical assessor comment on variability: the need to be aware of inter-subject variability is not considered applicable to the current product since dosing is based on amount of digoxin consumed: the need to be aware of intra-subject variability is not considered applicable to the current product since the product is given as a single dose.

Subpopulations: Renal impairment: *For proteins with MW lower than 50,000 Da, renal excretion is of importance for the elimination (increasing importance with lower MW) and consequently for the half-life of the protein. Thus, for these products pharmacokinetic studies in patients with renal impairment are recommended.*

Clinical assessor comment on subpopulations: the applicant has submitted an analysis of

subjects with "mild" renal impairment: this issue is addressed by wording in the proposed SPC. The applicant has not submitted data on other special populations such as subjects with hepatic impairment, children, women who are pregnant or lactating: these issues are addressed by proposed wording in the SPC and in the Risk Management Plan.

Clinical assessor conclusion on pharmacokinetic analysis submitted by the applicant: it may be concluded that the applicant has either (i) complied with the main body of advice in CHMP/EWP/89249/2004 Jan 2007 Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins or (ii) will seek to fulfil compliance by post-authorisation studies, as described.

Clinical assessor additional comment: the applicant has not provided information on the pharmacokinetics of the proposed product in the absence of digoxin.

Secondary objectives: ECG analysis

The applicant reports PTQ index as a surrogate estimate of digoxin concentration.

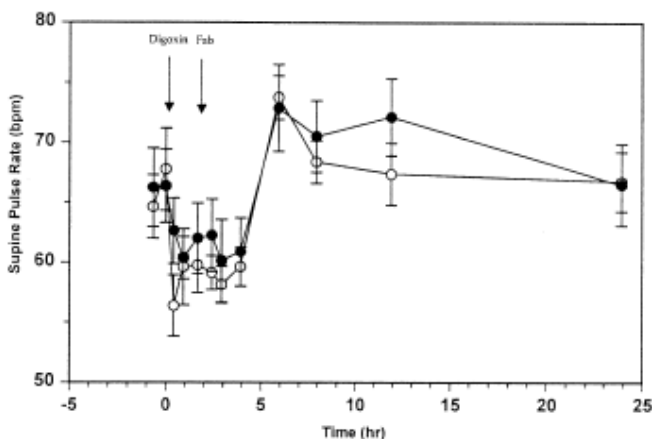
Clinical assessor comment: it is considered that the PTQ index, a derived parameter as described, does not add value to the measurement of free digoxin concentration.

Pharmacodynamic effects

Pulse rates: the applicant reports slowing of rate changes that may reflect digoxin infusion, as shown:

Figure 4. Pulse rate in the DigiTab group (●) and Digibind group (○)

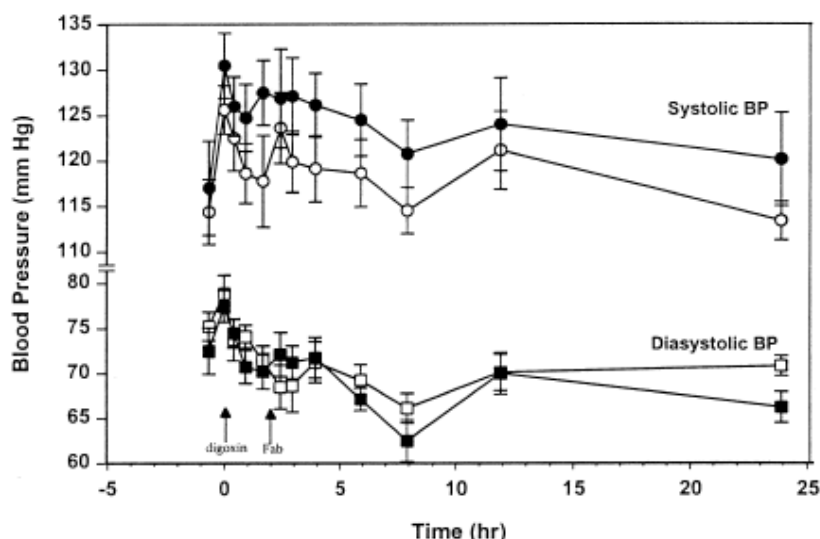
Results are average values in each group, \pm SEM.



Blood pressure measurements are as shown:

Figure 5. Supine systolic and diastolic blood pressure in the DigiTab group (●) and Digibind group (○)

Results are average values in each group, \pm SEM.



Clinical assessor comment: with regard to DigiTab: results presented suggest that pulse rate fell by (about) 5 bpm after infusion of digoxin (67 bpm before and 62 bpm after). Pulse rate was apparently not affected by infusion of DigiFab[®] until 4hr after end of infusion when the pulse rate was measured at (about) 72 bpm. Blood pressure is (apparently) unchanged. Results are consistent with (though not conclusive for) a pharmacodynamic effect of infusion of DigiTab mediated via reduction in free digoxin concentration.

Safety

Deaths

There were not any deaths in the study.

Immunogenicity

None of the subjects showed detectable human anti-sheep antibodies within the timeframe described

Adverse events

In the DigiTab group, 6 subjects reported 15 adverse events though 6 were related to digoxin infusion.

Those events that may have been associated with DigiTab were: tiredness, bloating, hypotension and phlebitis of the infusion vein. The applicant has supplied a narrative for each event.

Laboratory results did not shown any significant change.

Clinical assessor comment: the safety issues reported are acceptable/more information on immunogenicity would be preferred for the product as a whole.

Clinical assessor conclusion on study Tab007-02: IV DigiTab promptly reduces the concentration of free digoxin in the serum of healthy volunteers: the effect persists for up to 8hrs after which free digoxin can be detected up to the 24hr mark. By 48 hours, free digoxin is measurable at the lower limit of detection of the assay used. By visual inspection, the time course of results for free digoxin in serum reported for DigiTab are comparable to those achieved with Digibind.

With regard to pharmacokinetic data, it may be concluded that the applicant has either (i) complied with the main body of advice in CHMP/EWP/89249/2004 Jan 2007 Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins or (ii) will seek to fulfil compliance by post-authorisation studies, as described.

The applicant reports a terminal half-life of DigiTAb-digoxin of (about) 15hrs.

Results on pulse rate and blood pressure of subjects are consistent with (though not conclusive for) a pharmacodynamic effect of infusion of DigiTAb mediated via reduction in free digoxin concentration.

The safety issues reported are acceptable.

In view of the limited safety data and unpredictability of the onset and incidence of immunogenicity, post-marketing monitoring of adverse events and immunogenicity would be required.

I.1.2 Study TAb007-01

Study title: A trial to determine the safety, pharmacokinetics and pharmacodynamics of affinity purified, Digoxin Immune Fab, Ovine

Study number: TAb007-01

GCP certification: the applicant states that the study “was performed in compliance with Good Clinical Practice”. The sponsor provided a monitor to ensure compliance.

Ethical approval: the applicant states that the study was performed in accord with the Declaration of Helsinki, as described, and that the study was approved by local Institutional Review Boards. The applicant states that subjects were volunteers and signed a consent form.

Study design: an open-label, phase III multicentre study

The applicant has performed (i) *in vitro* radio-immunoassay saturation analysis and (ii) comparative tests to Digibind (GSK) to estimate that 1mg of the current product will bind 13µg of digoxin. Refer to accompanying Quality Assessment Report for further details.

Inclusion criteria:

The applicant states that the study population consisted of patients of any age and sex with potentially life-threatening cardiac rhythm disturbances with or without hyperkalemia and caused by digoxin intoxication. Intoxication may have resulted from either acute or chronic ingestion of any digitalis glycoside. Intoxication was further defined, and treatment indicated, for any one of the following conditions:

- electrocardiogram changes consistent with hyperkalemia in the face of digoxin toxicity.
- hemodynamic compromise associated with arrhythmias (e.g. bradycardia, high-grade atrioventricular blockade, extrasystoles).
- cardiovascular compromise requiring the use of catecholamines, atropine or intravenous antiarrhythmics.
- serum digoxin level greater than 4.5 ng/ml in normal or non-cardiac patients (i.e. patients free of underlying cardiac conditions such as atrial fibrillation or congestive heart failure) and clinical symptoms indicating digoxin toxicity.
- bradycardia, defined as (a) less than 40 beats per minute that is unresponsive to 1 mg of intravenous atropine sulfate; or (b) less than 60 beats per minute in patients with poor prognostic factors (e.g., cardiovascular or hemodynamic compromise).
- signs and symptoms of profound neurological abnormalities (e.g. obtundation, acute psychosis, disorientation to person place and time).
- a known ingestion in a child of greater than 0.1 mg/kg of digoxin or a steady state serum concentration of digoxin greater than 5.0 ng/ml and clinical symptoms indicating digoxin toxicity.

Clinical assessor comment: the main diagnosis to permit entry to this study, as stated, is life-threatening cardiac dysrhythmia caused by digoxin intoxication based on clinical decision making. Intoxication was further defined by the additional criteria listed above. Timing of measurement of serum digoxin in relation to intake of digoxin is not described (it is currently recommended that digoxin concentration should be measured at least 6 hours post-ingestion).

Exclusion criteria:

- current or prior treatment with Digibind or prior treatment with DigiTAB.
- current or planned use of any experimental medication or use of any experimental medication within four weeks prior to entering this study.
- inability to give informed consent as defined by criteria established by the Institutional Review Board (IRB) of the Investigators' institutions.
- known history of hypersensitivity to sheep-derived products except for minimal irritation reactions to sheep wool.
- previous enrolment in the current study.

Objectives:Overall trial objective:

- to evaluate the pharmacokinetics, pharmacodynamics and safety of DigiTAB in patients with digoxin toxicity (as compared to historical data of Digibind, GSK:).

Clinical assessor comment: the applicant states that the comparison to historical data was done in agreement with US regulatory authorities. The applicant has defined digoxin toxicity as co-existent ventricular arrhythmia or high-grade atrioventricular conduction block, usually in the face of hyperkalemia, and/or signs and symptoms of profound neurological abnormalities. It is noted that the applicant is concerned with digoxin toxicity as opposed to digitoxin.

Primary objective:

- to document the reduction of serum free digoxin to less than 0.5ng/mL by the end of the DigiTAB infusion (time "0" hours).

Secondary objectives:

- evaluation of clinical therapeutic response – i.e., pharmacodynamic response – as measured by the percent of patients showing resolution in digoxin-induced arrhythmias, high-grade conduction block, and/or severe neurological signs and symptoms at 2 and 4 hours after DigiTAB treatment.
- characterization of the pharmacokinetic disposition of digoxin and DigiTAB in patients with life-threatening toxicity as measured by total and free serum digoxin, total and free serum Fab, and urinary digoxin and Fab concentrations.
- characterization of other pharmacologic activity, e.g., clinical response profile as reflected by serum creatinine.

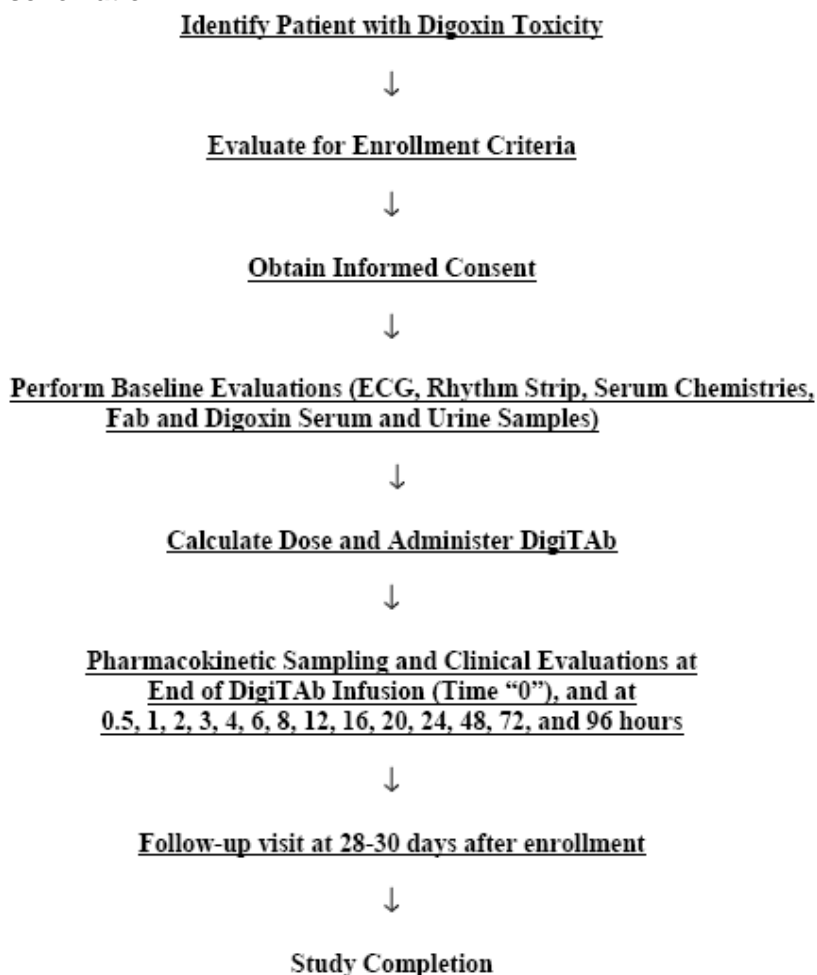
Tertiary objective:

- to assess the safety of DigiTAB

Protocol

An outline of the study flow is as shown:

Figure 6. Study schematic



Number of subjects studied: 15 subjects enrolled: 15 subjects completed observation for 24 hours in hospital: 10/15 subjects were evaluated at the 30 day follow-up (5 subjects were lost to follow-up).

Demographic data are given in table 3 below:

Table 3. Demographics

Demographic Parameter		(n = 15)
Age (years)	Mean	64 ± 15
	Median	67
	Range	40 – 85
Gender	Male	6 (40%)
	Female	9 (60%)
Weight (kg)	Mean	71.6 ± 20.4
	Male (mean, range)	82.7 (60.0 – 119.2)
	Female (mean, range)	64.2 (53.0 – 76.2)
Height (cm)	Mean	165 ± 9
	Male (mean)	172
	Female (mean)	160
Race	Caucasian	15 (100%)

Clinical assessor comment: the applicant states that 25 patients were planned for but that an agreement was reached with the (presumably US) regulatory authority that fewer subjects would be acceptable. All subjects were Caucasian with a mean age of 64yrs.

Clinical presentation of subjects

Digoxin ingestion was reported as chronic for 10 patients, suicidal for 5, acute on chronic for 3, acute for 1 and accidental for 1. Males accounted for 3 of the 5 suicidal ingestion cases while females accounted for 7 of the 10 chronic ingestion cases.

Nine patients had hemodynamic compromise as their digoxin intoxication manifestation upon enrolment.

Seven patients had a digoxin level >4.5 ng/mL, two of whom also had hemodynamic compromise.

All other digoxin toxicity manifestations occurred in conjunction with either of those two criteria plus one of the following: cardiovascular compromise, bradycardia and neurologic abnormalities.

Four patients had ECG changes consistent with hyperkalemia.

Results are summarised in the following table:

Table 4. Digoxin toxicity manifestations

Patient ID	Indicated Inclusion Criteria						
	ECG Changes	Hemodynamic Compromise	Cardiovascular Compromise	Digoxin Level >4.5 ng/mL	Bradycardia	Neurologic Abnormalities	Child - Known Ingestion
301			Yes	Yes		Yes	
302		Yes	Yes			Yes	
303		Yes	Yes			Yes	
401		Yes			Yes		
701		Yes					
702		Yes		Yes			
1101	Yes	Yes					
1102				Yes			
1103				Yes			
1104	Yes			Yes			
1105	Yes				Yes		
2001				Yes	Yes		
2002	Yes	Yes	Yes	Yes	Yes	Yes	
2101		Yes	Yes				
2201		Yes			Yes		

Reasons for being prescribed digoxin are shown in the following table:

Table 5. Digoxin therapy indications

Patient ID	Indication for Prescribed Digoxin Therapy			
	Not Prescribed Digoxin	Congestive Heart Failure	Atrial Fibrillation	Other Reason
301				Fast Heart Rhythm
302			Yes	
303				Fast Heart Rhythm and Coronary Artery Disease
401				Unclear
701		Yes		
702		Yes		
1101			Yes	
1102	Yes			
1103			Yes	
1104		Yes		
1105			Yes	
2001	Yes			
2002		Yes	Yes	
2101		Yes	Yes	
2201			Yes	

Clinical assessor comment: it is noted that only 9 subjects had haemodynamic compromise and only 7 had serum digoxin >4.5ng/mL (timing of measurement in relation to ingestion of digoxin is not stated). Cardiovascular compromise is described as 'requiring use of catecholamines, atropine or intravenous antiarrhythmics'.

The applicant states:

After initial evaluation (history, physical examination, electrocardiogram and the determination of baseline laboratory measurements) and informed consent, patients with potentially life-threatening digoxin toxicity were enrolled.

Each enrolled patient received an intravenous dose of DigiTab in an amount calculated to be approximately equimolar to the total body burden of digoxin based on either the serum concentration or known amount of digoxin ingested, as follows:

Calculation of total body burden of digoxin based on amount acutely ingested

Following an acute ingestion, the total body burden of digitalis is approximately equal to the amount of digoxin ingested in milligrams multiplied by the bioavailability (from the capsule) of 0.8.

Calculation of total body burden of digoxin based on based on serum concentration after acute or chronic ingestion

Total body burden of digoxin (mg) =
[serum digoxin concentration (ng/mL) x (5.6L/kg) x (patient weight in kg)] / 1000

If the amount ingested was not known or serum digoxin could not be measured then adults would be administered 20 vials (less for children).

Clinical assessor comment: the dosage estimate is based on a steady state volume of distribution of 5.6 L/kg for digoxin: this is advice given in the SPC for Digibind PL 00003/0207 (GSK). The calculation is based on population averages: errors will occur if non-steady state serum concentration of digoxin is measured or the individual does not conform to the 'average'. Use of correction factor 0.8 assumes that all subjects had taken capsules, as described, as opposed to elixir or other preparation. The applicant does not give information on timing of overdose in relation to hospital admission or on which DigiFab[®] calculation was used for each subject. Knowledge of timing is important because of the complex pharmacology of digoxin including the slow distribution in tissues. There were not any children in the cohort.

The applicant states that each 1mg of current product will bind 15µg of digoxin (later revised to 13µg of digoxin). The number of vials was calculated as (mg digoxin x 60 / 40). DigiTab was administered iv over 15–30mins. If toxicity was not reversed or appeared to recur then clinical judgement was used to administer further dosing.

Sampling

Blood samples were drawn immediately before infusion of the study drug, upon completion of the DigiTab infusion (time "0" hours) and at 0.5, 1, 2, 4, 6, 8, 12, 16, 20, 24, 36, 48, 72, and 96 hours after the end of the DigiTab infusion.

Urine was collected as a spot sample at baseline, and pooled collections at 0–12, 12–24, 24–48, 48–96 hours following DigiTab infusion.

Serum was analyzed for Fab and free and total digoxin. Urine collected through 24 hours was analyzed for free and total digoxin, and urine collected for 96 hours was analyzed for total Fab.

The applicant states that the lower limit of quantitation for free digoxin=0.3ng/mL.

Details on the methods of analysis are in the accompanying Quality Assessment Report.

Progress of subjects

Patients were monitored in the hospital for at least 24 hours. Serum and urine were collected to assess free and total digoxin and total Fab levels for the purposes of determining the pharmacokinetic parameters of DigiTab and digoxin. Serial ECGs, rhythm strips, vital signs, and

electrolyte measurements were collected to determine the pharmacodynamic effects of DigiTab. Patients were monitored for adverse events throughout the study.

Historical control comparisons were based on published data on the use of Digibind.

Efficacy

Results for primary objective: to lower free digoxin concentration, as described.

13/15 subjects had sufficient serum collected to permit analysis at time="0": 2 subjects had first samples taken at time=30mins. All subjects were analysed at time=30mins up to 24hrs as shown in the table below:

Table 6. Free digoxin levels in patients receiving DigiTab

Patient ID	Free Serum Digoxin Levels (ng/mL)											
	Base-Line	0.0 Hr	0.5 Hr	1.0 Hr	2.0 Hr	4.0 Hr	6.0 Hr	8.0 Hr	12.0 Hr	16.0 Hr	20.0 Hr	24.0 Hr
301	1.8	BLQ	BLQ	ND	BLQ	BLQ	0.4	0.5	0.7	0.8	0.7	0.5
302	2.5	BLQ	BLQ	BLQ	BLQ	0.3	0.9	1.0	1.2	1.4	1.5	1.4
303	2.8	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	1.4	2.3	1.9	2.3
401	3.4	BLQ	BLQ	BLQ	BLQ	BLQ	0.3	0.3	0.5	0.6	ND	0.7
701	1.5	BLQ	BLQ	BLQ	BLQ	BLQ	0.3	0.8	1.0	1.0	0.7	0.8
702	5.0	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	0.4	0.7	1.0	1.1
1101	1.3	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	0.5	0.6	ND	ND
1102	2.0	BLQ	BLQ	BLQ	BLQ	0.6	1.1	1.1	0.8	0.6	0.7	0.6
1103	5.0	BLQ	BLQ	BLQ	BLQ	0.9	1.7	2.1	1.6	1.9	1.3	1.2
1104	7.5	0.3	0.3	BLQ	0.3	1.3	2.1	2.2	2.8	2.4	2.3	2.4
1105	4.8	BLQ	BLQ	BLQ	BLQ	0.3	1.3	2	2.5	2.6	2	2.2
2001	13.0	BLQ	BLQ	BLQ	BLQ	BLQ	0.9	1.7	2.1	ND	ND	2.0
2002	3.1	QNS	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	0.3
2101	1.1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	0.3	0.4	0.4	0.4
2201	1.6	ND	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	0.3	BLQ
Median	2.8	BLQ	BLQ	BLQ	BLQ	BLQ	0.3	0.5	0.8	0.75	0.85	0.95

BLQ = below limit of quantitation

ND = Not Done

QNS = quantity not sufficient for analysis

Results of free digoxin assays in subjects up to 100hrs are presented in appendix 17.2.10 of the submitted report

Clinical assessor comment: all subjects had detectable free digoxin at baseline and all except 3 reported results of "BLQ" at time=0. 1 subject reported 0.3ng/mL (much lower than the starting figure of 7.5ng/mL) and 2 could not be assayed. 14 subjects reported "BLQ" at time=30mins, 1 had 0.3ng/mL at time=30mins. Serum free digoxin began to increase from 4–6hrs after finishing the dose of DigiTab. At 24hrs, all results remained lower than that obtained at baseline.

The stated primary objective of the study was to reduce free digoxin to less than 0.5ng/mL at the end of the infusion of product. It is considered that the applicant has met this primary objective.

Results for secondary objectives: clinical response, as described based on ECG and neurological status.

Investigators classified 6/15 subjects as having complete resolution of toxicity within 2hrs and 1 more within 3hrs of administration. 14 subjects had resolved by 20hrs. One subject was judged as a non-responder: the applicant notes that ECG abnormalities persisted in this subject at 30 day follow-up.

ECG: A blinded, independent, 3-member review panel provided consensus of ECG status and found that 8 subjects had "improved" by 2 hours and 10 subjects had "improved" by 4 hours.

5 subjects “worsened” from 6 hours onwards (in addition, 1 subject “worsened” at 1 hour and then “improved” and 1 subject pursued a fluctuating course from 0 to 24hrs). The applicant states that “worsening” may be due to recurrence of toxicity or removal of therapeutic effect of digoxin.

The applicant has supplied ECG analysis in appendix 17.2.8 of the submitted study report.

At 30-day follow-up, 7/10 subjects had ECG abnormalities similar to those recorded in hospital.

Clinical assessor comment:

Subjects who had not received DigiTab are not available for comparison: it is acknowledged that numbers of subjects are too small to have made meaningful comparison.

The ECG assessments are subjective. Nonetheless, the time course of changes suggests that it is credible that the ECG status reflected the free digoxin concentration resulting from product administration (and that worsening reflects either recurrent toxicity or removal of therapeutic effect). The time course of events would be similar to that described for Digibind (market leader at present).

7/10 subjects displaying persistent ECG abnormalities at 30 days reflects the high incidence of ECG abnormalities as a normal finding in this age group (and the difficulties faced when interpreting response to treatment)

The applicant has not made comment on neurological status.

Serum potassium concentration is recorded by the applicant: since subjects had chronic toxicity then hyperkalaemia would not be expected to be common to all: 6 subjects received potassium supplementation: the assertion by the applicant that serum potassium fell in response to treatment is not agreed based on the currently submitted data set although individual subjects did show a fall e.g subject 1105, $K^+ = 7.3 \text{ mEq/L}$ at time=0 and 4.9 mEq/mL at time=24hrs. In addition, hypokalaemia is reported for Digibind (current market leader).

Results for secondary objectives: pharmacokinetics for digoxin and DigiTab.

Digoxin

The applicant presents total digoxin concentrations: refer to table 12, page 36 of the study report. All subjects displayed a baseline digoxin concentration $>2 \text{ ng/mL}$ except for subject 701 who had 1.9 ng/mL .

Results of total digoxin assays in subjects up to 100hrs are presented in appendix 17.2.10 of the submitted report

The applicant states that the elimination half-life of digoxin in the presence of product= 22.8 ± 10.2 hrs: the applicant acknowledges that the data set is incomplete and not fully reliable.

Fab

The applicant considers that irregularities in the reported time curves for Fab measurement may reflect deficiencies in the method of storage of sample: the applicant concedes that reported values ought to be interpreted with caution. Nonetheless, the clearance of $33.9 \pm 23.1 \text{ mL/min}$ ($0.4 \pm 0.2 \text{ mL/min/kg}$) and half life of 16.9 ± 6.6 hrs are similar to results reported for study Tab007-02:

	clearance	Half life
Current study	$33.9 \pm 23.1 \text{ mL/min}$ ($0.4 \pm 0.2 \text{ mL/min/kg}$)	$16.9 \pm 6.6 \text{ hrs}$
Study Tab007-02	$32.0 \pm 6.5 \text{ mL/min}$	$15.4 \pm 3.8 \text{ hrs}$

Urine parameters were not assayed because of incomplete collections. Drug-drug interactions were not possible to evaluate because of the small numbers of participants.

The applicant presents the following pharmacokinetic data for the current product:

Table 7. FAB pharmacokinetic parameters

Subject	Weight (kg)	Dose (mg)	AUC _{0-∞} (ug/ml*hr)	AUMC _{0-∞} (ug/mL*hr ²)	CL (mL/min)	MRT (hr)	t _{1/2} (hr)	V _{ss} (L/kg)	C _{max} (ug/mL)	T _{max} (hr)
AJI 2101	70	45	47.6	994.1	15.8	20.6	24.2	0.3	8.2	1.0
BAS 1101	70.1	80	160.7	950.9	8.3	5.7	9.4	0.0	31.7	2.5
E-S 0302	61.7	40	72.5	1185.7	9.2	16.1	23.6	0.1	10.5	4.5
J-C 0301	117.9	200	40.1	491.7	83.2	12.0	15.8	0.5	15.4	0.5
KFH 1103	119.2	315	91.6	1772.3	57.3	19.1	26.7	0.6	36.9	0.5
HJK 2001	60	900	362.3	6857.1	41.4	18.7	27.6	0.8	118.0	0.5
KLR 1102	72	80	28.8	173.6	46.3	5.8	7.6	0.2	11.4	0.5
LLO 0702	62.5	160	ND	ND	ND	ND	ND	ND	39.6	0.5
MTA 2201	53	80	93.6	1020.8	14.2	10.7	15.3	0.2	21.2	1.0
P-B 0701	76.2	80	91.4	811.3	14.6	8.6	17.2	0.1	18.7	2.5
DJS 1105	57.3	80	ND	ND	ND	ND	ND	ND	ND	ND
RLB 0401	70	90	194.0	3223.8	27.8	16.4	10.7	7.7	14.1	1.5
LKL 1104	55.2	80	132.8	2015.4	36.1	14.9	15.8	9.0	20.5	0.5
MHM 2002	70	135	326.3	3152.4	24.8	9.4	13.8	3.9	42.7	0.5
SAS 0303	73.9	160	156.6	1633.8	61.3	10.2	11.9	10.4	33.3	0.5
mean	72.6	168.3	138.3	1867.9	33.9	12.9	16.9	2.6	30.2	1.2
SD	19.9	214.4	104.1	1759.1	23.1	5.0	6.6	3.8	27.8	1.2

Table 8. Clearance in mL/min/kg

Subject	Weight (kg)	CL (mL/min)	CL (mL/min/kg)
AJI 2101	70	15.8	0.23
BAS 1101	70.1	8.3	0.12
E-S 0302	61.7	9.2	0.15
J-C 0301	117.9	83.2	0.71
KFH 1103	119.2	57.3	0.48
HJK 2001	60	41.4	0.69
KLR 1102	72	46.3	0.64
LLO 0702	62.5	ND	ND
MTA 2201	53	14.2	0.27
P-B 0701	76.2	14.6	0.19
DJS 1105	57.3	ND	ND
RLB 0401	70	27.8	0.4
LKL 1104	55.2	36.1	0.7
MHM 2002	70	24.8	0.4
SAS 0303	73.9	61.3	0.8
Mean		33.9	0.44
SD		23.1	0.24

Clinical assessor comment: the applicant has returned results for half-life and clearance that are similar to those obtained from study on healthy volunteers.

The steady state volume of distribution results show wide variation: most results are 0.1–0.8 L/kg but the average is heavily skewed by 3 individuals with results between 7.7 and 10.4 L/kg. The applicant has not explored why these individuals demonstrated such heavily skewed results. Also, one subject returned an apparent result of 0 L/kg. It is considered that the results submitted by the applicant lack credibility without further explanation/justification and that the applicant may not make claims on the basis of these results.

Safety

Adverse events

58 adverse events were recorded (30 were recorded in one patient). The applicant considers that the following events, described in 6/15 subjects, may have been 'remotely related' to study medication:

- Chest pain, atrial fibrillation, pulmonary oedema, pleural effusion, worsening congestive heart failure, hypotension
- Disorientation, headache,
- Renal failure, hyperkalaemia, hypokalaemia, electrolyte disturbance
- Abdominal pain, constipation, nausea and vomiting

Most adverse events occurred in the days after infusion, as shown in the following table:

Table 9. Remotely related adverse events by patient and time post-infusion

<u>Patient (# of remotely related events/total events)</u>	<u>Time Post-Infusion</u>
401 (1/1 event) Moderate Chest Pain	3 days
702 (1/2 events) Mild Disorientation	2 days
1101 (9/30 events) Moderate Hyperkalemia Moderate Electrolyte Imbalance Moderate Hypokalemia Moderate Belly Pain Severe Pulmonary Edema Moderate Atrial Fibrillation Moderate Worsening Congestive Heart Failure Severe Bilateral Pleural Effusion Severe Renal Failure	Same day Same day 2 days 2 days 2 days and 16 days 5 days 2 days 7 days 14 days
1102 (2/4 events) Mild Hypokalemia Mild Headache	Same day 2 days
1103 (1/5 events) Mild Intermittent Constipation	4 days
1104 (3/5 events) Mild Hypotension Mild Nausea Mild Vomiting	1 day 1 day 1 day

Only one subject experienced a rash and that was not considered to be related to study medication.

Clinical assessor comment: The cardiovascular events may have been related to removal of digoxin from the system leading to worsening of heart failure. Delay in onset of adverse events up to 16 days has been described for Digibind (current market leader).

Death

There was one death during the trial: subject 2002 died of lung cancer: the death was not considered related to the study medication.

Serious adverse events

4 subjects experienced 5 serious adverse events: narratives are provided for 3 subjects on pages 46 to 48 of the study report. The applicant was either unable to ascertain causality or did not believe that the study medication was the cause. The events were pulmonary oedema, congestive heart failure, angina, palpitations and dyspnoea. Those subjects described were known to have pre-existing cardiovascular disease.

Additional safety parameters:

Laboratory results

Laboratory results are presented: the applicant has not done formal analysis

Physical examination/vital signs

Blood pressure and heart rate are presented: the applicant considered that changes were consistent with removal of digoxin

Immunogenicity

Data was collected on 2 subjects: results were below detection.

Post-marketing experience

The applicant states that the current product has been on the US market since 2002

Clinical assessor comment: no additional comment

Comparison with published results on similar products

The applicant claims that the current product exhibits similar safety data as reported for competing products.

Clinical assessor comment: no additional comment

Clinical assessor conclusion on study Tab007-01:

IV DigiTAb reduces serum free digoxin, as described, in 15 subjects who had been diagnosed with digoxin intoxication. The applicant presents data that suggest that features of digoxin toxicity were resolved after administration of DigiTAb although symptoms apparently re-occurred in some at 4-hours onwards: this may reflect underlying cardiac pathology revealed by removal of digoxin.

The applicant has not fully described the timing of DigiTAb in relation to ingestion of digoxin: the applicant has not described how DigiTAb dose was calculated for each individual patient (two formula are given): no children were treated.

7/10 subjects had abnormal ECGs at 30-day follow-up.

It is possible that some patients did not have digoxin intoxication at presentation.

For further assessment of comparison with historical data, refer to Statistics Assessment.

I.1.3 Study PR007-CLN-rpt003

Clinical assessor comment: Study PR007-CLN-rpt003 was conducted following discussion with MHRA.

Study title: Multicenter retrospective review of the clinical efficacy and safety of DigiFab® in digoxin poisoned patients

Study number: PR007-CLN-rpt003

GCP certification & ethics approval

The applicant states that the study “was performed in compliance with Good Clinical Practice” as described in document E6 of the ICH.

The applicant states that “All Investigation Review Boards granted an exemption from continuing IRB approval because the data existed at the time of data collection (retrospective study) and the collected data were de-identified..... to comply with applicable Health Insurance Portability and Accountability Act regulations”: refer to page 10 of the study report.

The applicant was permitted a waiver from informed consent because of the nature of the study: refer to page 10 of the study report.

The applicant states that the study was conducted in compliance with the Declaration of Helsinki (version not stated).

Clinical assessor comment: GCP and ethics statements are acceptable

Test product: DigiFab® (Digoxin Immune Fab (Ovine))

Study design: a phase IV study to carry out a retrospective review of existing medical records of life-threatening or potentially life-threatening digoxin toxicity or overdose

Number of subjects studied:

14 subjects enrolled and 14 subjects were analysed and included in the statistical analysis. The applicant states that sample size was based on discussion with the MHRA (UK).

Objectives

- to assess the effectiveness of DigiFab® in treating human patients with life-threatening digoxin toxicity
- to evaluate the safety of DigiFab® by characterizing frequencies and rates of drug-related adverse events

Inclusion criteria

- Patients of any age or gender, treated with DigiFab® between the January 1, 2003 and July 31, 2006.
- Serum digoxin level ≥ 2 ng/mL before the start of DigiFab® therapy
- Patient treated for one or more of the following life-threatening cardiac abnormalities, evident on ECG or rhythm strip (as determined by the consensus panel), within six hours before the start of DigiFab®:
 - i. Ventricular rate < 45 bpm
 - ii. 2nd degree heart block
 - iii. 3rd degree/complete heart block
 - iv. Asystole (ECG/rhythm strip may not be available)
 - v. Ventricular tachycardia (ECG/rhythm strip may not be available)
 - vi. Ventricular fibrillation (ECG/rhythm strip may not be available)

Exclusion criteria

- patient treated for intoxication of digitalis-containing compound other than digoxin purple foxglove, digitoxin)
- patients with a pacemaker prior to the start of DigiFab® (during baseline ECG)

Primary end-point

- rate of improvement in or resolution of life-threatening cardiac abnormalities by 72 hours after the end of treatment.

Clinical assessor comment: study objectives and inclusion/exclusion criteria are acceptable: it is noted that subjects with digitoxin intoxication were excluded.

Protocol

Medical records were identified from searches of the appropriate hospital pharmacy database(s) for all instances in which DigiFab® was dispensed between January 1, 2003 and July 31, 2006. Those records that matched the inclusion/exclusion criteria, as described, were taken forward. Only records from 2 of the named sites were used because of inclusion criteria.

Records were reviewed and consensus reached by an expert panel of board-certified physicians regarding the presence of one or more life-threatening cardiac manifestations from digoxin toxicity on baseline electrocardiograms (ECGs) or rhythm strip recordings. Panel members did not review data from his/her own institution. Majority vote was used if there was not agreement.

The applicant states that there was not any blinding of patients or investigators to treatment and that all pre-baseline (status of the patient during prior visit, when the patient was not in a digoxin toxic state) and post-treatment ECG and rhythm recordings were completely randomised to allow for blinded review by consensus panel members

The applicant states that all patients were treated with Digoxin Immune Fab (Ovine), DigiFab® a commercially available product in the United States, in accordance with standard of care. Doses administered to patients in this study varied from 2 to 7 vials as required (80 to 280mg product).

All medications administered to/by the patient prior to (from the time of presentation to the start of DigiFab® therapy), during, and up to 72 hours after DigiFab® treatment were recorded.

The following data were collected / tabulated:

- patient demographics (gender, age, ethnicity, type of ingestion, inclusion/exclusion criteria)
- medical and medication history
- digoxin therapy characteristics (digoxin prescription, co-ingestants)
- ECG and rhythm recordings (along with consensus panel identification of life-threatening abnormalities)
- digoxin-specific fab dosing (amounts, infusion period)
- concomitant therapies
- baseline and post- DigiFab® results for (as available):
 - laboratory measurements, including serum potassium and digoxin levels
 - clinical assessments of digoxin toxicity resolution (neurological, gastrointestinal, and general clinical response within 0 to 4 hrs, >4 to 12 hrs, >12 to 24 hrs, and >24 to 72 hours after the end of DigiFab® therapy)
- adverse events (categorized by relatedness and severity)

Subjects were assessed at 0–4hr, 4–12hr, 12–24hr and 24–72hr. Efficacy of DigiFab® was evaluated by assessment of 5 parameters, as described:

- gastrointestinal signs and symptoms
- neurological signs and symptoms
- general clinical disposition
- life-threatening cardiac rhythm abnormalities
all pre-baseline and post-treatment ECG and rhythm recordings underwent blinded review by the consensus panel as described. Consensus panel judgements were then unblinded. The applicant describes rules to achieve a decision where consensus was not reached.
- serum potassium concentration (described as improved if value 'normalised' after treatment)

Subjects were described as 'improved', 'worsened', 'unchanged' and 'no data' in comparison to data at baseline (prior to DigiFab®).

Clinical assessor comment: with respect to cardiac abnormalities, the applicant states that 'improved' equals no life-threatening cardiac rhythm abnormality present: it is considered that the applicant does not adequately state what 'life-threatening' would constitute or what threshold there is to make such a claim.

The following adverse events were recorded:

- gastrointestinal: nausea, vomiting, diarrhoea, abdominal pain, anorexia
- neurological: headache, visual disturbances, fatigue, dizziness, anxiety
- cardiovascular: hypotension, tachycardia, pulmonary oedema, congestive heart failure (exacerbation),
- genitourinary: renal failure, decreased urine output
- respiratory: chest tightness, bronchospasm, stridor
- skin/general: flushing, urticaria, non-urticarial rash, pruritus, angioedema, fever, malaise, hypokalemia
- others, as identified in the medical record

Total digoxin was measured prior to therapy but not free digoxin. Post treatment free digoxin was only measured in 2 subjects (free digoxin is not considered to be standard of care).

Each investigator was trained in data collection: an external audit of practice was carried out.

Results

Demographic data

Most subjects were elderly Caucasian, as shown:

Table 10. Demographic data

Variable	Measurement
Age (n = 14)	
Mean (\pm SD), years	71.3 (10.4)
Range, years	47 - 90
Gender (n = 14)	
# (%) of Males	7 (50)
# (%) of Females	7 (50)
Ethnicity (n = 14)	
# (%) African American	1 (7)
# (%) Caucasian	11 (79)
# (%) Unknown	2 (14)
Body Weight (n = 13, 1 unknown)	
Mean (\pm SD), kg	79.5 (20.1)
Height (n = 12, 2 unknown)	
Mean (\pm SD), cm	164.3 (14.6)

All subjects were taking digoxin for a prescribed indication prior to treatment, as shown:

Table 11. Prescribed dosage of digoxin and indications by patient

Patient ID#	Prescribed Dosage	Indication(s) for Taking Digoxin
01-001	0.25 mg daily	Atrial fibrillation, Congestive heart failure
01-004	0.25 mg daily	Atrial fibrillation
01-008	0.25 mg daily	Congestive heart failure
02-003	0.25 mg daily	Atrial fibrillation
02-008	0.125 mg daily	Atrial fibrillation
02-009	0.25 mg daily	Atrial fibrillation
02-018	Unknown	Atrial fibrillation
02-019	0.125 - 0.25 mg daily	Congestive heart failure
02-023	Unknown	Atrial fibrillation, Congestive heart failure
02-024	0.125 mg every 3 days	Atrial fibrillation
02-030	0.125 mg daily	Atrial fibrillation, Congestive heart failure
02-035	0.125 mg daily	Atrial fibrillation
02-038	0.25 mg daily	Atrial fibrillation
02-039	0.25 mg daily	Atrial fibrillation

Gender: M = Male, F = Female

All subjects were treated for overdose and all were diagnosed as occurring by unintentional, chronic exposure.

Efficacy

Baseline clinical findings are as shown:

Table 12. Baseline clinical effects of digoxin toxicity

Patient ID#	Cardiac Abnormality	Serum Digoxin (ng/mL)	Serum Potassium (mmol/L)	Gastrointestinal Effects (Y/N)?	Neurological Effects (Y/N)?
01-001	VR*	4.8	6.6 [†]	Y	Y
01-004	VR	5.2	5.3 [†]	N	Y
01-008	VR	3.4	7.3 [†]	Y	Y
02-003	VR*	6.5	5.6 [†]	N	Unknown
02-008	VR*	6.5	4.1	Y	Y
02-009	VR*	2.2	4.8	N	Y
02-018	HB3	2.7	5.6 [†]	Y	N
02-019	VR	3.3	6.4 [†]	Y	Y
02-023	VR*	2.2	4.5	N	Y
02-024	VR	3.4	4.6	Y	Unknown
02-030	VR*	2.3	5.2 [†]	Y	Y
02-035	VR*	3.1	6.1 [†]	N	Y
02-038	A*	2.2	4.9	N	Y
02-039	VR*	3.2	4.4	Y	Y

Cardiac Abnormalities: VR = Ventricular rate < 45 bpm, A = Asystole, HB3 = 3°/Complete heart block
 *An ECG recording from a prior, routine hospital visit (e.g., pre-baseline) was available in the medical record and no life-threatening rhythm abnormality was present
[†]Level was above the lab reference range (e.g., patient was hyperkalemic)
 Unknown = Not available as clinical effects could not be fully evaluated because patient was sedated

12 subjects had a slow ventricular rate <45bpm: the other 2 displayed (i) complete heart block or (ii) asystole. 8 were hyperkalaemic, 8 had gastro-intestinal symptoms, 11 displayed neurological symptoms (2 could not be evaluated because of sedation). 11/13 had a serum creatinine above the upper limit of the reference interval.

DigiFab® and concomitant medication administration up to 72hrs is as shown:

Table 13. Characteristics of DigiFab® administration and other concomitant therapies

Patient ID#	# of Doses of DigiFab	# of Vials of DigiFab (Fab dose, mg)	Duration of Infusion (min)	Concomitant Therapies (Before DigiFab)	Concomitant Therapies (During DigiFab)	Concomitant Therapies (After DigiFab)
01-001	1	4 (160)	30	Atr, G/I, F	None	None
01-004	1	4 (160)	30	Atr, F	None	G/I, Mg
01-008	1	5 (200)	30	Atr, G/ FI, V	V	V
02-003	1	2 (80)	Unknown	G/I, V	None	E
02-008	2 (28.5 hrs apart)	7 (280), 3 (120)	Unknown	F, Mg	None	Mg
02-009	1	2 (80)	Unknown	F	None	None
02-018	1	2 (80)	Unknown	E	None	E
02-019	1	3 (120)	Unknown	G/I,	None	P, F
02-023	1	2 (80)	Unknown	None	None	None
02-024	1	2 (80)	Unknown	F	None	E, F
02-030	1	1 (40)	Unknown	None	None	None
02-035	1	3 (120)	30	V	V	G/I, V
02-038	1	2 (80)	Unknown	None	None	None
02-039	1	1 (40)	30	Atr	None	None

Concomitant therapies: Atr = Atropine, G/I = Glucose/Insulin, P = Pacemaker, E = Enhanced elimination (Hemodialysis/Hemoperfusion), F = Fluid resuscitation, Mg = Magnesium, V = Vasopressor(s)

Most subjects received 2 vials: one subject received 7 vials. Known duration of infusion was 30mins (documented in only 5 subjects). Only 3 subjects did not receive additional therapy.

Clinical assessor comment: only 3 subjects did not receive additional therapy such as dialysis, atropine, fluid resuscitation etc. Glucose + insulin infusions would contribute towards resolution of hyperkalaemia. It is not possible to ascribe clinical improvement to DigiFab® alone or to know if DigiFab® contributed towards improvement.

The stated primary end-point was rate of improvement in or resolution of life-threatening cardiac abnormalities by 72 hours after the end of treatment. Rate was calculated as the number of patients with a value of “improved” divided by the number of patients with a value of “improved”, “unchanged”, or “worsened”. Patients with “no data” were not included in the denominator of any rate calculation.

The record of progress of resolution of heart rate as shown:

Table 14. Cardiac response to DigiFab® therapy. All responses are relative to baseline (baseline abnormalities are the same as those displayed in Table 12)

Patient ID#	Baseline	0 to 4 hrs	>4 to 12 hrs	>12 to 24 hrs	>24 to 72 hrs
01-001	VR	U	I	I	I
01-004	VR	U	ND	U	I
01-008	VR	I	I	I	I
02-003	VR	I	I	I	I
02-008*	VR	ND	U	U	I
02-009	VR	ND	ND	ND	I
02-018	HB3	ND	ND	I	I
02-019	VR	ND	ND	ND	ND
02-023	VR	U	I	I	I
02-024	VR	ND	ND	I	I
02-030	VR	ND	ND	ND	ND
02-035	VR	I	ND	I	I
02-038	A	ND	ND	ND	I
02-039	VR	U	U	ND	ND
# (%) Improved†	-	3/7 (43)	4/6 (67)	7/9 (78)	11/11 (100)

Cardiac Abnormalities: VR = Ventricular rate < 45 bpm, A = Asystole, HB3 = 3/Complete heart block

I = Improved, U = Unchanged, W = Worsened, ND = No Data Available

*Patient received a second dose of DigiFab 28.5 hrs after the end of the first dose

†Patients with no data (ND) were not included in the rate of improvement calculation for each interval

Clinical assessor comment: it is assumed that cardiac rate reflects ECG inspection (as opposed to bedside measurement): the applicant acknowledges that the data are incomplete e.g. 2 subjects did not have any data available after the first recording: the data are, at best, semi-quantitative and subjective. The method of calculating rate of improvement selects out those on whom measurements were obtained.

The applicant also presents heart rate (bpm) in table 12a of the report: it is noted that heart rates do not match those presented in table 4 above.

The applicant also presents tabulated data on gastrointestinal response, neurological response, general clinical disposition and serum potassium response: these are presented as secondary end-points All data sets are incomplete: refer to tables 3 to 8 of the submitted study report.

Clinical assessor comment: the applicant acknowledges that it is not possible to rule out that resolution of signs and symptoms was an effect of time i.e. via metabolism / elimination.

Safety

Adverse events recorded were as shown:

Table 15. Frequencies (percent) of adverse events by intensity and relatedness

Body System Adverse Event	Mild		Moderate		Severe		Total		Total
	R [†]	NR	R [†]	NR	R [†]	NR	R [†]	NR	R + NR
<i>Cardiovascular</i>									
Cardiac Arrest	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7)	0 (0)	1 (7)	1 (7)
Hypotension	0 (0)	1 (7)	0 (0)	0 (0)	1 (7)	0 (0)	1 (7)	1 (7)	2 (14)
Tachycardia	0 (0)	0 (0)	1 (7)	1 (7)	0 (0)	0 (0)	1 (7)	1 (7)	2 (14)
TOTAL	0 (0)	1 (7)	1 (7)	1 (7)	1 (7)	1 (7)	2 (14)	3 (21)	5 (36)
<i>Gastrointestinal</i>									
Abdominal Pain	0 (0)	0 (0)	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	1 (7)	1 (7)
Anorexia	0 (0)	1 (7)	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	2 (14)	2 (14)
TOTAL	0 (0)	1 (7)	0 (0)	2 (14)	0 (0)	0 (0)	0 (0)	3 (21)	3 (21)
<i>Neurological</i>									
Anxiety	0 (0)	0 (0)	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	1 (7)	1 (7)
Fatigue	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7)	1 (7)
Pre-syncope	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7)	1 (7)
TOTAL	0 (0)	2 (14)	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	3 (21)	3 (21)
<i>Respiratory</i>									
Bronchospasm	0 (0)	0 (0)	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	1 (7)	1 (7)
Respiratory	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7)	0 (0)	1 (7)	1 (7)
Failure	0 (0)	0 (0)	0 (0)	1 (7)	0 (0)	1 (7)	0 (0)	2 (14)	2 (14)
TOTAL									
<i>Skin/General</i>									
Fever	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7)	1 (7)
TOTAL	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7)	1 (7)
TOTAL	0 (0)	5 (36)	1 (7)	5 (36)	1 (7)	2 (14)	2 (14)	12 (86)	14 (100)

[†]R = related = definitely or possibly related to DigiFab therapy

One event of tachycardia and one event of hypotension was considered to be related to DigiFab®.

Clinical assessor comment: it is acknowledged that the numbers of subjects are too small to make meaningful conclusions on the adverse events.

It is noted that 11/13 subjects had a raised serum creatinine at the first measurement on entry: at the final post-treatment measurement this was 4/11. There were not any reports of anaphylactic reactions or anaphylactoid reactions.

Deaths

There were 2 deaths, both at more than 5 days after the end of administration of DigiFab®: narratives of the deaths are provided: the applicant considered that neither death was caused by DigiFab®.

Clinical assessor comment: it is acknowledged that the deaths occurred in subjects with known severe disease unrelated to digoxin therapy.

The clinical expert for the applicant states that the efficacy objectives of the study were achieved: resolution of life threatening cardiac abnormalities 72 hours after treatment was demonstrated in all 11 of the evaluable data sets and that evaluable data sets showed resolution of the secondary endpoint variables within in 86–100%.

The clinical expert for the applicant acknowledges that adverse events were too few to make meaningful conclusions.

Clinical assessor comment: the assertion of the clinical expert with regard to efficacy is not agreed: because of incomplete data, co-existing medical conditions and concomitant treatments, it

is not possible to ascribe clinical improvement to DigiFab® alone or to know if or how much DigiFab® contributed towards clinical improvement.
The assertion of the clinical expert for the applicant with regard to adverse events being too few to draw meaningful conclusions on safety is agreed.

Clinical assessor conclusion on study PR007-CLN-rpt003: the data submitted are too few, incomplete, subjective/semiquantitative and affected by concomitant medication: it is not possible to ascribe clinical improvement to DigiFab® alone or to know if or how much DigiFab® contributed towards clinical improvement. There are not enough data to make meaningful conclusions on safety. It is considered that deficiencies of the current study, as described, reflect upon the nature of the study rather than upon the current product.

II. Statistics assessment of bioequivalence and efficacy

Trial TAb 007-02

This trial included 16 healthy volunteers, 8 randomised to each of DigiTAB and the comparator Digibind.

The goal of the trial was to demonstrate comparable bioaffinity of digoxin between the experimental digoxin immune Fab, DigiTAB, and the commercially available Digibind.

Volunteers in both treatment groups received 1 mg of digoxin in 8 ml of sterile water. The digoxin infusion was administered during the protocol time -5 min to 0 hours.

Two hours after the end of the digoxin infusion, eight volunteers received 76 mg of Digibind and the other eight received 76mg of DigiTAB intravenously over 30 minutes.

To measure free digoxin, blood samples were collected at the following time points: immediately before infusion of the digoxin, upon completion of the digoxin infusion (time zero), and at 30 minutes, 1, 2, 2.5, 3, 4, 6, 8, 12, 24, and 48 hours after the digoxin infusion. Hence 8 measurements (starting from the 2.5 hour time-point) were taken after administration of Digibind or DigiTAB.

The primary efficacy parameter was the area under the free digoxin concentration-time curve (AUC) from 2 hr (start of the DigiTAB/Digibind infusion) to the last measurement at 48 hr. Low concentrations represent better bioaffinity.

The pattern in both treatment groups was that the free digoxin concentrations dropped below the level of quantification for all patients at the first post-treatment measurement. The concentrations then remained low throughout the study, with DigiTAB and Digibind patients having a mean of 2.5 and 1.9 observations respectively above the limit of quantification with a C_{max} of 0.6 ng/mL in both groups.

The applicant provides values for the AUC imputing 0.3 ng/mL for all data points below the level of quantification. However these values do not mean a great deal as almost all the data are imputed.

It is clear that in both groups the levels were reduced to almost zero for the duration of the trial and that subsequently a similar small rebound occurred in both groups.

It is not really possible to statistically analyse this data as almost all the observations were below the level of quantification. It can only be said that both treatments were extremely effective at reducing serum free digoxin levels.

Trial TAb 007-01

This trial recruited 15 patients with potentially life-threatening cardiac rhythm disturbances caused by digoxin intoxication. The study was designed to demonstrate that administration of DigiTAb to patients experiencing digoxin toxicity would reduce serum free digoxin levels to lower than clinically meaningful concentrations (<0.5 ng/mL). A secondary efficacy parameter was clinical therapeutic response, as measured by the percent of patients with resolution of digoxin-induced toxicity at two and four hours following DigiTAb administration.

Serum samples for determination of free digoxin were drawn by the Investigator's staff immediately prior to DigiTAb administration and upon completion of DigiTAb infusion, and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 20, 24, 48, 72 and 96 hours after the end of the DigiTAb infusion.

The primary objective in this study was reduction of free serum digoxin concentrations to less than 0.5 ng/mL at "0" hours (end of Fab infusion). Thirteen patients in this study had sufficient serum collected at this time point. In all 13 patients, free serum digoxin concentrations decreased to at or less than the assay limit of quantitation (0.3 ng/mL) after Fab infusion. Two patients did not have a serum digoxin sample collected until 0.5 hours after Fab infusion; both of these patients' serum free digoxin concentration at this time was less than 0.3 ng/mL.

Investigators classified 6 of 15 patients (40%) as having complete resolution of digoxin toxicity within 2 hours of DigiTAb administration, with one additional patient resolving by 3 hours. Digoxin toxicity resolution was maintained in these 7 patients (47%) at 4 hours. Fourteen patients (93%) were classified by investigators as having resolved their digoxin toxicity by 20 hours.

The comparisons with historical data are not particularly useful. The data were collected in the early 1990s when the background treatment available may have been very different. As such it is not clear that the patients in the historical trials are comparable with the patients recruited into the trial. There are further problems in that detailed baseline characteristics are not available for the historical controls, and even the dosing regimen is not known.

Hence we can see that DigiTAb does not appear to be notably inferior to the treatments used in the historical control trials, but we cannot make any strong efficacy conclusions based upon this information.

Overall statistical conclusion

In every patient administered DigiTAb in both trials serum free digoxin was reduced to below the level of quantification immediately after treatment. If reduction of serum free digoxin levels is a good surrogate for clinical therapeutic response then efficacy has been established. It is clear that such reductions would not occur in untreated patients.

However if assurance is needed that DigiTAb has a similar performance to other treatments in obtaining clinical therapeutic response in patients, further data are required. These would ideally be in the form of a trial directly comparing DigiTAb to a reference product in patients with digoxin intoxication, allowing a direct comparison of therapeutic response rates. Historical control trials are not enough.

III. Pharmacovigilance system and risk management plan

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The applicant has provided a Risk Management Plan that is considered to adequately monitor identified and potential risks in relation to suspected adverse reactions.

IV. PRODUCT LITERATURE

SmPC

The applicant has adopted posology as recommended by the UK National Poisons Information Service, as described.

Patient information leaflet

The applicant has adopted the preferred wording as described. The PIL was accompanied with readability test to fulfil the requirements of article 59(3). The layout and design of PIL are acceptable. Key safety messages are clearly displayed. The user test was satisfactory. Based on this, the PIL for DigiFab® is considered to be approvable.

Label

Enclosed and no comments suggested.

V. OVERALL CONCLUSION

V.1. Risk-benefit assessment

Benefits

General benefit

Digoxin toxicity is life-threatening. Conventional treatment has been to stop intake of digoxin and correct electrolyte disturbance and acid-base imbalance: the long half-life of digoxin of 20–40 hrs leads to a prolonged period of management. Administration of digoxin antibodies will promptly lower the concentration of biologically-active digoxin and so lead to a speedier resolution of the overdose.

Efficacy

The applicant has presented data that suggest that the current product lowers free digoxin concentration in serum of healthy volunteers in a time course and to a similar extent as the current market leader in the UK, Digibind (GSK). The applicant has presented data of use in 15 subjects in the USA who had been admitted to hospital with digoxin overdose. Results indicate that the free digoxin concentration in serum of subjects with digoxin overdose was lowered to the same extent as would be expected with the current market leader in the UK, Digibind (GSK).

Safety

The applicant has proposed a registry of subjects who receive the current product for digoxin overdose. It is considered that a registry would improve knowledge of effectiveness and safety/immunogenicity of the current product. The applicant will adopt/adapt posology as recommended by the UK National Poisons Information Service. Patient information text will also include contact phone numbers for the UK National Poisons Information Service: this service offers Consultant-led advice on management of subjects with digoxin toxicity.

Risks

Efficacy

The applicant's data set on the pharmacokinetics and pharmacodynamics of the current product is limited for healthy volunteers and patients with digoxin overdose including those with cardiac compromise. There is not any information on special populations i.e. children, hepatic failure, pregnant women.

Safety

The applicant has not submitted data on immunogenicity post-administration. The applicant has not described subjects who have received the current product for separate instances of digoxin overdose: it is not known to what extent subjects may be sensitised.

The data set on adverse events during/after administration of the current product is very small (23 subjects only).

V.2. Balance of benefit v. risk

It is acknowledged that digoxin toxicity (to the degree that warrants administration of digoxin antibodies) is not common and that the applicant would experience difficulties in recruiting adequate numbers of subjects in order to pursue formal randomised, controlled trials of the current product. The applicant has agreed to an acceptable list of post-approval commitments regarding the outstanding data on quality (Module 3). It is understood that the current UK market leader, Digibind (GSK), will be withdrawn from the UK market place in the next months. It is understood that the current product would be the only alternative.

V.3. Conclusions

The overall benefit-risk assessment may be regarded as positive and the application may be granted.

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of DigiFab® are well defined and controlled. The applicant has agreed to an acceptable list of post-approval commitments regarding any outstanding data.

NON-CLINICAL

In view of the information available from the published literature further non-clinical studies may not be required. It is sufficient to draw conclusions concerning the efficacy or safety of DigiFab® from the clinical data.

EFFICACY AND SAFETY

Clinical data were submitted and considered adequate to draw conclusions on the efficacy and safety of DigiFab. A post-authorisation registry of subjects will be conducted.

The SmPC, PIL and labelling are acceptable.

BENEFIT-RISK ASSESSMENT

The applicant has adequately addressed the deficiencies in the information on the current product. The benefit-risk balance is, therefore, considered to be positive.

DigiFab[®], 40mg/vial digoxin immune Fab, powder for solution for infusion
(digoxin immune Fab [ovine])
PL 21744/0001

STEPS TAKEN FOR ASSESSMENT

- 1 The MHRA received the marketing authorisation application 1st of September 2004
- 2 Following standard checks the MHRA informed the applicant that its application was
considered valid on 28th of April 2006
- 3 The application was referred to the Commission on Human Medicines (CHM) for
advice at its meeting in July 2007
- 4 Following assessment of the submitted data, several requests for supplementary
information were sent to the applicant and several responses received between the
28th March and the 9th May 2011
- 5 The application was referred to the Commission on Human Medicines (CHM) for
advice at its meeting on 12th May 2011
- 6 A teleconference was held between the applicant and the MHRA on the 13th May
2011
- 7 The CHM sent a list of conditions for approval to the applicant in a letter dated 17th
May 2011
- 8 Following assessment of the submitted data, a further request for supplementary
information was sent to the applicant on 17th June 2011
- 9 The applicant submitted its response to the supplementary information request in a
letter dated 30th June 2011
- 1 0 The application was finalised on 1st July 2011

DigiFab[®], 40mg/vial digoxin immune Fab, powder for solution for infusion
(digoxin immune Fab [ovine])

PL 21744/0001

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

Summary of Product Characteristics (SmPC)

DigiFab[®], 40mg/vial digoxin immune Fab, powder for solution for infusion

(digoxin immune Fab [ovine])

PL 21744/0001

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

DigiFab[®], ▼ 40 mg/vial digoxin immune Fab, Powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each glass vial of DigiFab[®] contains 40 mg of digoxin immune Fab (ovine) protein as a sterile, lyophilized, off white powder.

For a full list of excipients see Section 6.1

3 PHARMACEUTICAL FORM

Powder for Solution for Infusion

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

DigiFab[®] is indicated for the treatment of known (or strongly suspected) life-threatening digoxin toxicity associated with ventricular arrhythmias or bradyarrhythmias unresponsive to atropine where measures beyond withdrawal of digoxin and correction of serum electrolyte abnormalities are considered necessary.

4.2 Posology and method of administration

It is advised to discuss management of patients with digoxin toxicity with the UK National Poisons Information Service at the following contact phone number: 0844 892 0111

Management follows a step-wise decision process, as shown:

Step 1	Decide if digoxin poisoning is (i) acute, (ii) acute-on-chronic or (iii) chronic.
Step 2	Is the patient (i) an adult or a child >20 kg or (ii) a child <20 kg?
Step 3	Is (i) the amount of digoxin ingested known or is (ii) the serum concentration of digoxin known?

Step 1 (i) Acute digoxin poisoning

Half the estimated dose required for full neutralisation can be given initially followed by monitoring for 6-12 hours if there is a full response. The remainder may be given if there is no clinical response within 2 hours.

Rationale: in acute digoxin poisoning, the serum digoxin concentration does not reflect total body load and complete neutralisation is not necessary in digoxin-naïve patients.

Step 1 (ii) Acute-on-chronic digoxin poisoning

A full neutralisation dose of DigiFab® can be given if the amount of digoxin ingested is known. If the amount of digoxin ingested is not known then a half-neutralising dose of DigiFab® based on serum digoxin concentration should be used followed by monitoring for 6-12 hours if there is a full response. The remainder may be given if there is no clinical response within 2 hours.

The usual dose for adults and children over 20 kg may vary between one half of a vial (20 mg DigiFab®) to 20 vials (800 mg DigiFab®). More vials may be needed dependent upon the amount of digoxin consumed.

Step 1 (iii) Chronic digoxin poisoning

Half the estimated dose required for full neutralisation can be given initially followed by monitoring for 6-12 hours. The remainder may be given if there is recurrence of toxicity.

Rationale: in chronic digoxin poisoning, the dose of antibody required for full neutralisation depends on the total body load of cardiac glycoside which has to be counteracted. However, as these patients are receiving digoxin therapeutically, full neutralisation is not necessary.

Dose calculation for full neutralisation in digoxin poisoning:

Step 2 (i) Adults and children > 20 kg	
Step 3 (i)	<p>Dose of digoxin ingested known</p> <p>Full neutralisation dose of DigiFab® is:</p> <p>Number of vials = Amount of digoxin ingested (mg) x 1.6</p> <p>Round up to the nearest vial</p> <p>To calculate the number of milligrams to be prescribed: multiply the number of vials by 40 (as there are 40 mg/vial).</p>
Step 3 (ii)	<p>Serum digoxin concentration known</p> <p>Full neutralisation dose of DigiFab® is:</p> <p>Number of vials = [serum digoxin concentration (ng/mL) X weight (kg)] / 100</p> <p>Round up to the nearest vial</p> <p>To calculate the number of milligrams to be prescribed: multiply the number of vials by 40 (as there are 40 mg/vial).</p>

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Step 2 (ii) Children <20 kg	
Step 3 (i)	<p>Serum digoxin concentration known</p> <p>Full neutralisation dose of DigiFab® is:</p> <p>Number of vials = $[\text{serum digoxin concentration (ng/mL)} \times \text{weight (kg)}] / 100$ </p> <p>Round up to the nearest vial</p> <p>To calculate the number of milligrams to be prescribed: multiply the number of vials by 40 (as there are 40 mg/vial).</p>
<p>Step 3</p> <p>Alternate for children <20kg when serum digoxin not known</p>	<p>Serum digoxin concentration not known</p> <p>One vial of DigiFab® will usually be sufficient for full neutralisation.</p>

Converting units of digoxin ng/mL to / from nmol/L

ng/mL (or µg/L) x 1.28 = nmol/L

nmol/L x 0.781 = ng/mL (or µg/L)

Method of administration

DigiFab® should be reconstituted prior to administration according to the instructions provided in section 6.6.

The final solution of DigiFab® should be infused intravenously over a 30 minute period.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients.

4.4 Special warnings and precautions for use

UK National Poisons Information Service

It is advised to discuss management of patients with digoxin toxicity with the UK National Poisons Information Service at the following contact phone number: 0844 892 0111

General management of patients

Dosage estimates are based on a steady-state volume of distribution of 5 L/kg for digoxin in order to convert serum digitalis concentration to the amount of digitalis in the body. These volumes are population averages and vary widely among individuals.

Ordinarily, improvements in signs and symptoms of digoxin toxicity begin within 30 minutes following administration of DigiFab®.

Patients should have continuous electrocardiographic monitoring during and for at least 24 hours after administration of DigiFab®. Temperature, blood pressure and potassium concentration should be monitored during and after DigiFab® administration.

Patients previously dependent on the inotropism of digoxin may develop signs of heart failure when treated with DigiFab®. After successful management of poisoning, digoxin has had to be reinstituted in some cases.

If, after several hours, toxicity has not adequately reversed or appears to recur, re-administration of DigiFab® at a dose guided by clinical judgement may be required.

Failure of the patient to respond to DigiFab® should alert the physician to the possibility that the clinical problem may not be due to digoxin toxicity.

Suicidal ingestion may involve more than one drug. Toxic effects of other drugs or poisons should not be overlooked, particularly where failure to respond to DigiFab® raises the possibility that the clinical problem is not caused by digoxin intoxication. If there is no response to an adequate dose of DigiFab®, the diagnosis of digoxin toxicity should be questioned.

There is no information on re-administration of DigiFab® to patients for a second (or more) episode of digoxin toxicity.

Risk of infusion-related reactions or hypersensitivity

As with any intravenous protein product, infusion-related reactions or hypersensitivity reactions are possible. It is recommended that patients are monitored for signs and symptoms of anaphylaxis and an acute allergic reaction. Medical support must be readily available when DigiFab® is administered.

If an anaphylactic reaction occurs during an infusion then administration of DigiFab® must be stopped immediately.

The likelihood of an allergic reaction may be higher in subjects who:

- are allergic to sheep-derived proteins (as may be found in cheeses and meats). DigiFab® is produced from sheep protein.
- are allergic to papain, an extract of the papaya fruit. Papain is used to cleave the whole antibody into Fab and Fc fragments: traces of papain or inactivated papain residues may be present in DigiFab®. Papain shares allergenic structures with (i) chymopapain and other papaya extracts, (ii) bromelain found in pineapple, (iii) dust mite allergens and (iv) latex allergens.

Impaired renal function

It may be expected that excretion of the Fab-digoxin complexes from the body is slowed in the presence of renal impairment and that digoxin may be released after some days from retained Fab-digoxin complexes.

Impaired hepatic function

There is no information on the use of DigiFab® in subjects with hepatic impairment.

Laboratory tests

Digoxin assay kits may not be able to measure accurately digoxin concentrations greater than 5 ng/mL (6.4 mmol/L). Exercise caution when using digoxin concentrations above these figures to calculate the dose of DigiFab® required.

Presence of the exogenous antibody fragments will interfere with immunoassay measurements of digoxin. The total serum digoxin concentration may rise precipitously following administration of DigiFab® but this will be almost entirely bound to the Fab fragment and therefore not able to react with receptors in the body.

General handling

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Repeated use

There are not any data on repeated dosing of DigiFab®. Repeat dosing with DigiFab® may give rise to an anaphylactic reaction. Repeat dosing must only be done when it is considered that clinical benefit outweighs risk.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of DigiFab® in pregnant women. The use of DigiFab® should be considered only if the expected clinical benefit of treatment to the mother outweighs any possible risk to the developing foetus.

Lactation

It is not known whether DigiFab® is excreted in human milk

A risk to the suckling child cannot be excluded.

Breast-feeding should be discontinued during treatment with DigiFab®

Fertility

There are no fertility data

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Adverse reactions reported from 23 subjects in clinical studies are listed below according to system organ class.

Adverse reactions are ranked by frequency, the most frequent first, using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$) very rare ($< 1/10,000$), including isolated reports.

Exacerbation of low cardiac output states and congestive heart failure or a rapid ventricular response in patients with atrial fibrillation may occur owing to withdrawal of effect of digoxin.

Adverse reactions may occur up to 14 days after the infusion has been administered.

System organ class	Frequency	Undesirable effect
Metabolism and nutrition disorders	Common	Hypokalaemia, hyperkalaemia
Nervous system disorders	Common	Headache, confusional state
Gastrointestinal disorders	Common	Nausea, vomiting, diarrhoea, constipation, abdominal distension
Cardiac disorders	Common	Worsening of cardiac failure Chest pain Hypotension Orthostatic hypotension
Musculoskeletal and connective tissue disorders	Common	Influenza-like illness
Renal and urinary disorders	Common	Renal failure
General disorders and administration site conditions	Common	Fatigue Infusion site phlebitis

4.9 Overdose

No case of overdose has been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: VO3A B24 Digitalis antitoxin

DigiFab[®] has a high affinity for digoxin.

DigiFab® binds digoxin and so reduces the concentration of free digoxin.

When DigiFab® is administered to a patient with digoxin toxicity, there is a reduction in the serum concentration of free digoxin leading to a reduction in toxicity.

5.2 Pharmacokinetic properties

In a study of healthy volunteers who were administered 76 mg of DigiFab® iv 2 hours after 1 mg digoxin iv, the serum elimination half-life of DigiFab® was (about) 15 hours.

5.3 Preclinical safety data

There are no preclinical safety data of relevance to the prescriber that are additional to safety data already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate
Acetic acid
Mannitol

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years
From a microbiological point of view, the product should be used immediately after reconstitution.

6.4 Special precautions for storage

Store between 2 & 8°C. Do not freeze.
Keep vial in outer carton in order to protect from light.
For storage conditions of the reconstituted medicinal product see section 6.3

6.5 Nature and contents of container

Single clear, neutral glass vial closed with a butyl rubber stopper and fitted with an aluminum flip top seal. One glass vial containers in an outer pack.

6.6 Special precautions for disposal

Instructions for Disposal

Any unused product should be disposed of in accordance with local requirements.

General Instructions

For single use only. Use immediately after reconstitution. The reconstituted solution should be a clear to slightly opalescent, colourless to pale yellow solution.

Method of Preparation for Administration

Each vial should be reconstituted with 4 mL of sterile Water for Injection by gentle mixing. This produces an approximately isosmotic solution with a protein concentration of 10 mg/mL that may be diluted further to any convenient volume with sterile saline suitable for infusion.

7 MARKETING AUTHORISATION HOLDER

Protherics UK Limited
Blaenwaun, Ffostrasol,
Llandysul, Ceredigion, SA44 5JT

8 MARKETING AUTHORISATION NUMBER(S)

PL 21744/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/07/2011

10 DATE OF REVISION OF THE TEXT

01/07/2011

Patient Information Leaflet

DigiFab, 40mg/vial digoxin immune Fab, powder for solution for infusion

(digoxin immune Fab [ovine])

PL 21744/0001

Patient Information Leaflet

DigiFab[®], 40 mg/vial digoxin immune Fab, Powder for solution for infusion (referred to as DigiFab[®] hereafter in this leaflet).

Read all of this leaflet carefully before you are given this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

In this leaflet:

1. What DigiFab[®] is and what it is used for
2. Before you are given DigiFab[®]
3. How DigiFab[®] will be given
4. Possible side effects
5. How DigiFab[®] will be stored
6. Further information

1. WHAT DIGIFAB[®] IS AND WHAT IT IS USED FOR

DigiFab[®] belongs to a group of medicines known as digitalis antitoxins. It is a preparation of protein fragments derived from antibodies produced in sheep. DigiFab[®] binds and neutralises digoxin.

DigiFab[®] solution is used to treat an overdose of digoxin when stopping taking digoxin and other measures are not sufficient.

2. BEFORE YOU ARE GIVEN DIGIFAB[®]

You should not be given DigiFab[®] if you are hypersensitive to DigiFab[®] or to any of the other ingredients of DigiFab[®] (for other ingredients see section 6 Other information).

Take special care with DigiFab[®]. Before you take DigiFab[®] you should tell your doctor if:

- You are allergic to papaya extracts, to pineapple or to sheep proteins (sheep protein may be found in cheeses and some meats).
- You are taking digoxin for heart problems. DigiFab[®] neutralises digoxin and may cause a worsening of your heart condition).
- You have been treated previously with DigiFab[®]. Repeat use of DigiFab[®] may be associated with a severe hypersensitivity reaction.

If any of the above apply to you then talk to your doctor who will decide what to do.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast feeding

There is no information on the use of DigiFab[®] in pregnant women or women who are breast feeding. If you are pregnant, likely to become pregnant or are breast-feeding then you must tell your doctor before taking this medicine. Your doctor will have taken this into account before giving DigiFab[®].

Driving and using machines

There is no information on whether DigiFab[®] affects the ability to drive or operate machines. Ask your doctor for advice.

3. HOW DIGIFAB[®] WILL BE GIVEN

Your doctor or nurse will usually give you DigiFab[®] by infusion into a vein. The powder in each vial will be dissolved in sterile water and may be further diluted with sterile saline solution.

Your doctor will calculate the amount of DigiFab[®] that you will be given depending on how much digoxin you have in your body. The usual dose for adults and children over 20kg may vary between one half of a vial (20mg DigiFab[®]) to 20 vials (800mg DigiFab[®]).

You will be monitored with blood tests and continuous heart monitoring during DigiFab[®] treatment and for at least 24 hours after DigiFab[®] treatment has been finished.

If you think you have been given too much DigiFab[®]

If you think you have been given too much DigiFab[®] tell a doctor or nurse or pharmacist immediately.

If you have further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, DigiFab[®] can cause side effects, although not everybody gets them.

The following side effects are important and will require immediate action if you experience them. Tell your doctor or nurse immediately if you experience any of the following symptoms (you may need to stop DigiFab[®]):

- a sudden allergic reaction with shortness of breath, rash, wheezing and drop of blood pressure
- allergic skin reactions such as rash, itchy skin, hives
- fever

The frequencies at which the above reactions occur are not stated. The following side effects have also been reported:

Common, affecting up to 1 in 10 people:

- Worsening of heart failure causing retention of fluid
- Chest pain
- Low blood pressure
- Changes in blood test results for potassium (this may affect how the heart works or cause tiredness, weakness or pins and needles)
- Severe kidney disease
- Light-headedness on standing
- Inflammation of vein at site of infusion
- Flu-like symptoms
- Headache, feeling confused, feeling tired
- Nausea, vomiting, diarrhoea or constipation, abdominal distension

Symptoms may occur up to 14 days after the infusion.

If any of the side effects gets serious, or you notice any side effects not mentioned in this leaflet, please tell your doctor or nurse.

5. HOW DIGIFAB[®] IS STORED

You will be given DigiFab[®] in a hospital. The hospital will store the medicine correctly between 2 and 8°C. Not to be stored in a freezer.

After DigiFab[®] has been made up, it should be used immediately.

DigiFab[®] must not be used after the expiry date on the vial and outer carton. The hospital pharmacist will check this before he/she dispenses DigiFab[®].

All medicines should be kept out of the reach and sight of children.

6. FURTHER INFORMATION

What DigiFab[®] contains

- The active substance is digoxin immune Fab.
- The other ingredients are sodium acetate, acetic acid and mannitol.

What DigiFab[®] looks like and contents of the pack

DigiFab[®] is supplied as a sterile, off-white powder in a clear glass vial, closed with a rubber stopper and aluminium flip top seal. Each vial contains 40mg digoxin immune Fab protein.

Each pack contains 1 vial.

Marketing Authorisation Holder and Manufacturer

The marketing authorisation holder is Protherics UK Limited, Blaenwaun, Ceredigion SA44 5JT, UK.

This leaflet was last approved in July 2011

Labelling

**DigiFab[®], 40mg/vial digoxin immune Fab, powder for solution for infusion
(digoxin immune Fab [ovine])**

PL 21744/0001

CARTON TEXT

<p>For single use only. Reconstitute with 4 mL of water for injection and use immediately. DigiFab[®], 40 mg/vial digoxin immune Fab, Powder for solution for infusion should be given by a medical practitioner. For further information see the enclosed leaflet. Store between 2-8°C in the original container. Do not freeze. Keep out of the reach and sight of children.</p>	<p>DigiFab[®], 40 mg/vial digoxin immune Fab, Powder for solution for infusion</p> <p>For Intravenous Use</p> <p>Do not use after the expiry date shown on the carton and the vial.</p>	<p>DigiFab[®], 40 mg/vial digoxin immune Fab, Powder for solution for infusion</p> <p>For Intravenous Use</p> <p>1 Vial</p> <p>Each vial of powder for solution for infusion contains 40 mg of digoxin immune Fab. Also contains sodium acetate, acetic acid and mannitol.</p>	<p>DigiFab[®], 40 mg/vial digoxin immune Fab, Powder for solution for infusion</p> <p>For Intravenous Use</p> <p>1 Vial</p> <p>PL Holder Protherics UK Limited Ffostrasol, Llandysul, SA44 5JT PL Number 21744/0001</p> <p>Distributed by Beacon Pharmaceuticals Ltd, 85 High Street, Tunbridge Wells, TN1 1YG</p> <p>POM</p>
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LID

<p>DigiFab[®], 40 mg/vial digoxin immune Fab, Powder for solution for infusion</p> <p>For Intravenous Use</p> <p>1 Vial</p>
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BASE

<p>BN</p> <p>Exp.</p>

VIAL TEXT

<p>DigiFab[®], 40 mg/vial digoxin immune Fab, Powder for solution for infusion</p> <p>For Intravenous Use</p>	<p>Store between 2-8°C. Do not freeze</p> <p>Protherics UK Limited</p> <p>BN: Exp.</p>
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