

Isolagen BLA: Dr. Witten Briefing Meeting 4-30-09

Participants

Celia Witten, Terrig Thomas, Patrick Riggins, Michael Yao, Agnes Lim, Yao-Yao Zhu, Atm Hoque, Shiojzen Lee, Alan Ou, Janet White, Lori Tull

The minutes from the filing meeting held 4-17-09 were provided as a starting point for discussion

1. Administrative – (Lori)

- eRoom update – Lori created a folder in the Regulatory Management Staff eRoom for STN 125348 and will make sure that all team members have access to that eRoom.
- Briefing Dr. Midthun – Dr. Witten or Steph will provide updates to Dr. Midthun at Office Directors meetings up to the mid-cycle review date when a briefing document will be sent.
- The mid-cycle review is set for August 3rd. Lori requested that all review team members try to keep this date available, and to update their Outlook calendars well in advance with vacation dates that fall around this time.

2. Discussion regarding acceptability for filing – (All)

- Checklists – all review team members received the checklist templates except Randa Melhem who was recently assigned by DMPQ. Lori will send the template to her.
- Refuse to File Deficiencies – **No RTF deficiencies were found for any of the modules. The Review team concurred to recommend filing of the BLA.**
- Review issues – a number of issues were raised that need to be addressed during the review cycle.
 - Dr. Witten asked if there any product issues related to filing of the BLA. Dr. Thomas stated that there were no RTF issues. The only concern is their lack of a good potency assay, but they had implemented the Agency's suggestion of including the collagen production assay.
 - Dr. Witten was informed about the use of (b)(4) IRB by Isolagen, but that no studies related to the BLA were currently open. Dr. Witten was also informed that Isolagen is not currently manufacturing any product, and they would need to be doing this before the facility inspection.
- Filing letter due May 5th, 2009 – Completed filing templates to be sent to Lori ASAP

3. Advisory committee (OCTGTAC) discussion – (All)

- Areas of concern for Isolagen based on examination of CDRH Medical Devices Advisory Committee - General and Plastic Surgery Devices Panel meeting November 18-19, 2008

- Committee composition
 - It was agreed that the list of panel members for the above CDRH AC meeting could provide some members for the Isolagen AC, but that other members with experience in the cell therapy field would also be required.
 - From the list of panel members that have served on various CDRH ACs, Dr. Witten recommended including Dermatologist Amy Newburger. She did not think the materials/engineering/implant specialist Stephen Li would be appropriate for the Isolagen AC panel.
 - Dr. Witten suggested contacting Susan Walker (Division Director – Division of Dermatology and Dental Products at CDER) and David Kraus (Branch Chief, Plastic and Reconstructive Surgery Devices Branch at CDRH) as consults in planning the AC.
 - Also, Dr. Witten reminded the Review Team that the statistical reviewer Shiohjen Lee has also been involved in reviewing Dermal Filler Devices while at CDRH.
- Sponsor notification – Not discussed at this time
- FR Notice – Not discussed at this time.

Action Items

- A monthly meeting schedule will be set up to allow for discussions of particular issues that arise during the review cycle. Separate meetings will be arranged to discuss the AC meeting agenda/questions
- Inspections

Timing for DMPQ originally planned to be in late August, but as this will be close to the mid-cycle review phase, it was suggested that the inspection occur in late September to mid-October, before the advisory committee meeting in November.

 - Dr. Witten strongly recommended that the AC take place in October, if possible, as following the AC there could be unforeseen action items that may need to be addressed and that November and December are difficult months to get things done expeditiously. She suggested contacting Gail Dapolito to find out the available dates ASAP.

5-1-09 - The next scheduled CTGTAC is Nov. 5-6, 2009

- Product reviewer credentialing – still to be done

Clinical Discussion

Overview of Safety across Trials – Presented by Yao-Yao Zhu

Summary of Safety

- Most events were common injection site reactions
- 1 instance of severe injection site ischemia after the third treatment in an IT-treated subject -----(b)(6)-----
- 4 SAEs that were considered unrelated to IT

- 3 subjects discontinued from the study due to an AE: injection site pain, breast cancer and fatigue syndrome
- Safety analyses: Performed on all patients who received at least one study treatment (Safety Population)

1. Safety database

- Number of subjects: 508 patients from seven trials
- Type of subjects: 20 to 77 years old, 92% female, and 92% White, with moderate to severe nasolabial fold wrinkles
- Extent of exposure: a total dose between 2.5 and 3.5 ml of isolagen therapy at $1-2 \times 10^7$ cells/ml, intradermal, one to three treatment at an interval of one to six weeks
- No severe adverse events related to IT
- Most of AEs were unrelated or unlikely to be related to the study treatment
- Most events were common injection site reactions

Summary of treatment-emergent events reported in >1% of patients

	N%	
	IT (N=508)	Placebo (N=354)
Injection Site Redness	81 (16%)	33 (9%)
Injection Site Swelling	69 (14%)	15 (4%)
Injection Site Pain	31 (6%)	6 (2%)
Injection Site Edema	22 (4%)	0
Injection Site Nodule	20 (4%)	3 (<1%)
Acne	8 (2%)	1 (<1%)
Application Site Papules	8 (2%)	0

2. Severity of Adverse Events:

- Majority of AEs: mild to moderate
- IT injection is less tolerated than placebo injection

Severity of the AEs	IT, n (%) (N=508)	Placebo, n (%) (N=354)
Administration site condition	343 (68%)	144 (41%)
Mild	283 (56%)	131 (37%)
Moderate	55 (11%)	12 (3%)
Severe	5 (<1%)	1 (<1%)

3. Relationship to the Study Treatment

- Common, local injection site reactions: possibly, probably or definitely related to the product injection
- Other types of events: unrelated

4. Deaths: two death, unrelated to the study treatment

- A 57 yo female patient died of myocardial infarction after three treatment with placebo
- A 77 yo female patient died of cardiac arrest prior to treatment with study drug

5. Previous commerce experience/anecdotal reports

- US experience
 - From 1995 to 1999, 1200 patients were treated, 200 physicians used IT, no documented significant AEs.
 - mild to moderate IT injection site reaction: redness, swelling, rash, splotching and pruritus
 - One case of herpes outbreak after injection
 - No nodular hypertrophy, skin sloughing, infection, lumps, scarring
 - Most significant finding: local redness/edema > 3 days; redness/induration for 10 days
- UK experience
 - From 2002 to 2007, 6000 patients were treated
 - Injection site redness, swelling and lump
 - All AEs resolved 7 days to 5 months,
 - Three treated-related SAEs: angioedema, severe allergic reaction and lump requiring surgical remove of the scar

6. Clinical laboratory evaluation

- Clinical labs were performed in studies IT-R-001 and IT-R-002 and were not performed in other 5 trials
- Lab parameters: chemistry, liver function test, lipid profile, uric acids, complete cell count
- No significant abnormality, no discernable trends

7. Vital signs, physical findings, other safety monitoring:

- no clinically significant differences

8. Safety Conclusions

- A transient or minimal swelling, mild redness, and discomfort at the treatment site immediately following injection
- Mildly less tolerated than the placebo injection
- IT is a safe and effective treatment for nasolabial fold wrinkles.
 - Dr. Witten asked whether there were any issues with regard to Pharmacovigilance.
 - Alan Ou (OBE) said that the pharmacovigilance plan (PVP) was somewhat vague and although not a filing issue it needs to be improved upon during the review cycle. Although there are no identified safety risks with the Isolagen product a risk evaluation and mitigation strategy (REMS) may be warranted based on potential risks.
 - Given that the demographic for the pivotal studies was 20 to 77 years old, 92% female, and 92% White, Dr. Witten asked whether any consideration

had been given to post-marketing studies to represent other groups. This should be discussed further during the AC planning.

- Dr. Witten asked about the photographic scale used to measure efficacy, whether subject photos had been submitted to the BLA and if so how would the clinical reviewers use this information. Michael Yao thought the photographic data had been submitted, but was not sure. Dr. Witten said she had asked the question because it had become an issue during review of Dermal Fillers at CDRH. For example, if subject photos are provided, do you look at all of them and if so what are you looking for. Are baseline photos also provided?
- Dr. Witten asked whether there were any financial conflicts of interest for any of the PIs on the pivotal studies. Michael Yao noted that while some PIs were previously paid as consultants for Isolagen they were not paid for taking part in the pivotal studies.
- Dr. Witten asked whether there were any significant differences in the efficacy data from the “consultant” PIs compared to the other PIs. Shiohjen Lee said that there was no apparent difference in the efficacy data between the two groups.
- Dr. Witten asked whether there were any discrepancies between the number of subjects enrolled, number of biopsies processed and number of product lot failures? I informed her that there were very few product lot failures. The clinical team had not looked at the data in sufficient detail to identify reasons for patients enrolling but not undergoing treatment. Dr. Witten suggested that during the BiMo inspections the enrollment logs and screening logs should be examined. She would be interested to know how many patients were accepted in to the study, but the biopsy was not accepted for manufacture.
- Dr. Witten asked for another briefing meeting with the same group sometime in mid- to late June.

Follow-up e-mail sent by Dr. Witten 5-1-09

Thanks for the briefing yesterday. I have a few suggestions: Regarding the question I asked, how would you label or describe the results if a fair number of people are manufacturing failures, this is a topic that Winitsky recently presented to an IOM Committee looking at missing data issues. It could be useful to get one of them on board as a consultant, either now or in the review process. Winitsky would know who the committee was, but probably we would want to let Temple and O'Neill know we wanted to pursue this, since it is directly touching upon the committee work there.

Also, we may want to get someone on board from CDRH and Derm to do a consult, not a whole review, but ask them some focussed questions and touch base informally to see if they have any other thoughts. Questions could include for example: what do they think we should do with the photos or what do they think of post-market issues given the population demographic.