

REGULATORY CONSIDERATIONS FOR THE TREATMENT OF LIPODYSTROPHY

REPORT OF A FORUM FOR COLLABORATIVE HIV RESEARCH
ROUNDTABLE DISCUSSION
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FORUM FOR COLLABORATIVE HIV RESEARCH

DEPARTMENT OF PREVENTION AND COMMUNITY HEALTH
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ACKNOWLEDGMENTS

This Roundtable was organized by the Forum for Collaborative HIV Research, an independent public/private partnership that receives core operational funding from government agencies and industry. The recommendations of the Roundtable were presented at the 6th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV on October 27, 2004, in Washington, DC.

The Forum is deeply grateful to the chair of this project, Dr. William Powderly, for his leadership of the project and skillful moderation of the roundtable. The Forum also specifically thanks Dermik Laboratories and Serono Laboratories for their support of this meeting.

We are also especially grateful for the contribution of the government and industry presenters. (Please see Appendix A for the full agenda). Finally, the success of the workshop depended on the active participation of each of the participants listed in Appendix B – the Forum thanks all of them for their contributions of questions, ideas, experience, and support.

A special thank you goes to the project coordinator, Houtan Mova. Without his expert coordination and support, the project would not have become a reality.

On October 25, 2004, the Forum for Collaborative HIV Research sponsored a roundtable discussion entitled *Regulatory Considerations for the Treatment of Lipodystrophy*. The roundtable was convened to bring regulators, clinical investigators, HIV patient advocates, and industry representatives together to address issues related to designing clinical trials of treatments and interventions for lipodystrophy. The goals of the roundtable were to:

1. review the types of lipodystrophy,
2. recommend methods of objective and subjective measurement,
3. recommend entry criteria for clinical trials based on the type of lipodystrophy,
4. recommend the degree and duration of response that would merit regulatory approval of a treatment or intervention, and
5. assess any additional endpoints that might be required for the approval of a treatment or intervention.

The roundtable focused on the fat redistribution aspect of lipodystrophy syndromes in adults; definition of lipodystrophy syndromes, metabolic changes associated with the lipodystrophy syndromes, or lipodystrophy in children and adolescents were not discussed.

For purposes of defining entry criteria and measuring response to therapies for lipodystrophy, roundtable participants agreed on four distinct clinical types: facial atrophy, peripheral atrophy, visceral adiposity, and dorsocervical fat pads.

- Clinical trials should be designed as prospective, randomized studies with randomly assigned treatment lasting for at least 6 months.
- Longer periods of randomly assigned treatment may be needed as more treatments become available.

- Drug studies that rely on quality-of-life measures should have a placebo control.
- Endpoints should be comparable across studies, such as standardized photography compared by means of a standardized grading scale to document changes in facial lipoatrophy.
- All endpoint measures, including quality-of-life scales, should be obtained with validated methods.

Facial Lipoatrophy:

- Entry into a clinical trial should be decided by patient and physician based on subjective determination of the presence of facial lipoatrophy not caused by HIV wasting.
- Effectiveness of treatment should be based on (1) objective measurements of fat restoration, e.g., by ultrasound and photograph; and (2) subjective determination of satisfactory improvement on the part of the patient and physician. Durability of response should be assessed with at least 2-year studies.
- Safety of treatment will be assessed on a case-by-case basis and dependent on the class of drug or type of intervention.

Peripheral Lipoatrophy

- Entry into a clinical trial should be decided by patient and physician, most likely based on a subjective determination of peripheral fat loss and, if possible, an objective DEXA measurement indicating less than 8 kg of peripheral limb fat or a 25% loss of limb fat compared to population normal values (although normal values are not available for all population types).
- Effectiveness of treatment should be based on objective DEXA measurements. The percentage of increased fat that will indicate effectiveness of a treatment will depend on the baseline value.

- Safety evaluations should demonstrate no worsening of visceral adiposity or metabolic parameters (e.g., lipid profiles or glucose intolerance).

Visceral Adiposity

- Entry into a clinical trial should be based on objective waist circumference and waist-to-hip ratio measurements and, to a lesser extent, on patient and physician selection based on a subjective determination of increased truncal fat. Early trials should recruit subjects with body mass indices in the overweight or obesity range.
- Effectiveness of treatment should be based on CT scans at the L4-L5 level (a direct measure of visceral adipose tissue [VAT] and the preferred measurement), DEXA scans (a measure of truncal fat, i.e., VAT plus subcutaneous abdominal fat), and objective anthropometry, such as waist-to-hip ratio. Induction of satisfactory efficacy after at least 3 months of treatment and durability of efficacy after at least 6 additional months of treatment should be demonstrated. Inclusion of quality-of-life outcomes assessed by *validated* instruments is strongly recommended. All studies should be placebo controlled.
- Safety evaluations should demonstrate no worsening of peripheral lipotrophy, percentage of lean body tissue, and metabolic outcomes (e.g., no worsening of baseline glucose intolerance), and, hopefully, should demonstrate an improvement in baseline dyslipidemia.

Dorsocervical Fat Pad

- Entry into a clinical trial should be based on patient and physician agreement that treatment is indicated to relieve physical or psychological discomfort.
- Effectiveness of treatment should be based objectively on a reduction in the measured size of the fat pad and, in symptomatic patients, subjectively on an improved quality of life.

INTRODUCTION

With the expanded use of potent antiretroviral therapies, people with HIV infection are living longer and thus exposed to a greater risk of experiencing treatment related adverse events. The lipodystrophy syndrome comprises a group of side effects that may threaten the long-term success of antiretroviral therapy. Studies have demonstrated a significant psychological and emotional impact caused by body fat redistribution, including forced disclosure of HIV infection, depression, decreased self-esteem, problems in social and sexual relations, and noncompliance with antiretroviral regimens.

Concerns for fat redistribution and metabolic abnormalities were raised as early as 1997.¹ The underlying mechanisms and causes are still unclear, and definitions of lipodystrophy syndromes are still evolving.²⁻⁴ Nevertheless, there has been a strong focus on managing objective and subjective symptoms of the syndrome associated adverse events collectively or individually. Some of the approaches have included changing antiretroviral regimens,⁵ providing nutrition and exercise counseling,⁶ intervening surgically,⁷ and prescribing symptomatic therapies, such as statins,⁸ recombinant human growth hormone (r-hGH),⁹⁻¹¹ and metformin.¹² Most studies of these interventions have had relatively small sample sizes and short durations, so the ability to generalize results and the durability of effect are unknown.

Currently, there is no consensus on appropriate surrogate markers to measure in clinical trials addressing lipodystrophy related events, what the magnitude of change and the durability of surrogate marker changes should be, and what other endpoints might be required for clinical studies. The purpose of the roundtable was to begin to address the issues of appropriate clinical trial design to further the development of successful treatments and interventions for lipodystrophy. The roundtable focused on the fat redistribution aspect of lipodystrophy syndromes; it did not discuss the etiology of lipodystrophy syndromes, their definitions, or the metabolic changes associated with the lipodystrophy syndromes.

OBJECTIVES AND GOALS

The roundtable was convened to bring regulators, clinical investigators, patient advocates, and industry representatives together to address issues related to designing clinical trials of treatments and interventions for lipodystrophy. The goals of the roundtable were to:

- 1) review the types of lipodystrophy,
- 2) recommend methods of objective and subjective measurement,
- 3) recommend entry criteria for clinical trials based on the type of lipodystrophy,
- 4) recommend the degree and duration of response that would merit regulatory approval of a treatment or intervention, and
- 5) assess any additional endpoints that might be required for the approval of a treatment or intervention.

FDA PERSPECTIVE

Dr. Jeffrey Murray began with an overview of the United States Food and Drug Administration (FDA) branches that are involved in the licensing of drugs and interventions, and the types of endpoints assessed for evaluations of safety and efficacy. Dr. Robert Perlstein followed with a discussion of the evaluation of r-hGH in lipodystrophy treatment. Dr. Herbert Lerner and Cdr. Stephen Rhodes followed with a discussion of the evaluation of the FDA-approved injectable filler, poly-L-lactic acid (PLLA, Sculptra™ or New-Fill™), for facial lipoatrophy.

REGULATORY JURISDICTION

Antiretroviral agents are evaluated and reviewed at the FDA by the Center for Drug Evaluation and Research (CDER), Division of Antiretroviral Products. Some drugs to treat lipodystrophy (such as r-hGH) are evaluated and reviewed by the Division of Metabolic and Endocrine Drug Products. Interventions, such as injectable fillers, implants, and plastic surgery, are evaluated and reviewed in the Division of General, Restorative and Neurological Devices. Evaluation of lipodystrophy treatments and interventions will likely require cross-communication between these divisions.

DRUG SAFETY AND EFFICACY ENDPOINTS

In the treatment of HIV/AIDS, the overall risk/benefit is of primary concern. Thus, safety claims for new drugs are evaluated in the context of the safety of drugs already available. This includes changes in metabolic parameters, such as changes in lipid, glucose, and insulin levels to assess dyslipidemia and glucose intolerance. Changes in body morphology associated with lipodystrophy (e.g., central adiposity, peripheral and facial lipoatrophy, weight gain, cervicodorsal fat pad, and gynecomastia) are evaluated by physical examination as well as radiographically

(e.g., dual-energy x-ray absorptiometry [DEXA], computed axial tomography [CT], magnetic resonance imaging [MRI] scans, and ultrasonography). Routine laboratory evaluations, such as liver function tests, renal function tests, and hematologic parameters are monitored as well.

A comparative claim for a decreased de novo incidence of lipodystrophy or a reduction in preexisting lipodystrophy will not be possible until there is an accepted definition for the term. However, comparisons may be drawn based on the effect on specific components of the syndrome, i.e., decreased de novo or reduced preexisting facial atrophy, peripheral atrophy, or abdominal hypertrophy. An example of data that supports a comparative labeling claim for a new antiretroviral drug is the data from Bristol-Myers Squibb study AI424-043 that showed lower levels of low-density lipoprotein cholesterol (LDL), total cholesterol, and triglycerides, but no decrease in high-density lipoprotein cholesterol (HDL) levels, in patients treated for 24 weeks with atazanavir (Reyataz®) compared to those treated with lopinavir/ritonavir (Kaletra®).¹³

Approval of agents or interventions for lipodystrophy will also be based on their overall risk/benefit as indicated by their efficacy and safety as determined by multiple endpoints. Objective measures of fat gain or loss will be measured based, for instance, on changes in visceral abdominal fat on CT scans, changes in truncal fat and total body fat on DEXA scans, and skinfold thickness measurements. These measures are not yet clinically validated and will need to be supported by subjective endpoints, using such tools as validated quality-of-life or body image questionnaire or photographs.

ENDPOINTS FOR GROWTH HORMONE-RELATED PRODUCTS

The FDA recently reviewed an industry sponsored phase II lipodystrophy study in which r-hGH was successfully used to first induce and then maintain a reduction in visceral adipose tissue (VAT) and truncal adiposity, measured by CT scan and DEXA scan, respectively. The dose of r-hGH used during the 12-week induction phase of the phase II study was reduced to 4 mg/day due to the increased incidence of glucose intolerance/diabetes mellitus in earlier studies using a dose of 6 mg/day.

Based on encouraging results from this study, the sponsor and the endocrine division at CDER agreed on a phase III study protocol specifying 4 mg/day of r-hGH to be administered during the 12-week induction phase and 2 mg every other day to be administered during a 24-week maintenance of effect/durability phase. The phase III study was powered based on an expected decline of 8% in VAT (measured by CT scan) during the induction phase (a compromise between the 10% reduction in VAT observed during the phase II trial described above and a 5% reduction derived from CDER's obesity guidelines). The endpoint agreed to for the maintenance phase was that fewer than half the subjects would gain back more than 50% of the VAT lost during the induction phase. Secondary endpoints included changes in truncal fat, total body fat, limb fat, and lean body mass (all measured by DEXA scan), and changes in scores derived from validated quality-of-life and body self-image questionnaires. Of note, the FDA considers quality of life to be an extremely important, supportive, secondary efficacy endpoint. Safety assessments were to include the means and distribution of the insulin-like growth factor I (IGF-I) response standard deviation score (SDS) -- with an SDS value greater than +2 considered to be potentially deleterious, comprehensive evaluation of the glycemic response, complete lipid profiles, and the incidence of de novo tumors. Long-term measures in future studies should include carotid artery ultrasound and cardiac adverse events, with appropriate diagnostic expertise provided by cardiologist/radiologists.

ENDPOINTS FOR INJECTABLE FILLERS

In August 2004, the FDA approved the use of injectable PLLA (poly-L-lactic acid) for the treatment of facial lipoatrophy. PLLA was approved first in Europe, then by expedited FDA review in the United States through the FDA's program for review of drugs approved by the European Medicines Evaluation Agency (EMA). The approvals were based on single investigator and multicenter clinical trials performed in the U.S. and Europe. Safety was assessed on the basis of adverse events reported in patient diaries, CD4 counts, and lactic acid levels. Efficacy was assessed by photography and measurements of skin thickness using ultrasound and calipers. Subjects had Fitzpatrick I through VI skin types. (The Fitzpatrick scale runs from I – fair skin that burns easily to VI – darkly pigmented skin). The longest pre approval follow-up was 2 years. The sponsor is conducting a post approval study to collect 5 year follow up data and to include at least 30 females and 30 subjects with Fitzpatrick skin types IV-VI.

In completed studies, improvement in facial fullness reached its maximum in 25 weeks. Concerns regarding potential keloid formation as a result of treatment have been expressed. Although there were no data on keloid formation from these studies, some unseen, palpable subcutaneous nodules were reported.

Validation of skin thickness measurement techniques is an important issue. Discussions are underway at the FDA regarding the use of calipers in measuring skin thickness. Ultrasound, another approach to skin thickness measurements, is also not yet validated for this use. Data from studies in which ultrasound was used to measure diabetic foot ulcers are available and may be useful, but these have not been submitted to the FDA. The reproducibility of various measurement methods is operator dependent; consistency in the placement of facial measurements is very important. Although the patient photographs provided startling evidence of effect, the use of this tool is not yet standardized either. Thus, determination of the best

measurement tools and their validation remain key issues for the choice of entry criteria and endpoints in clinical trials assessing lipodystrophy interventions.

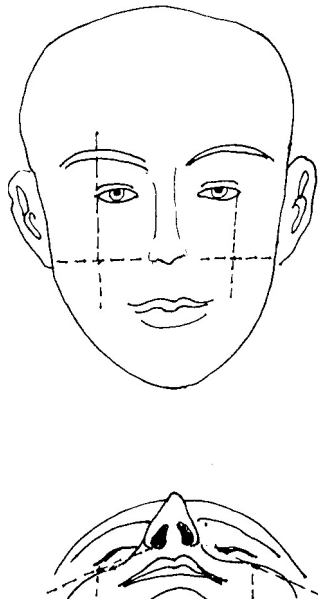
Dr. Sharon Levy reviewed the experience of Dermik Laboratories with PLLA, a drug the company acquired after it was developed in Europe. Dr. Norma Muurahainen from Serono Laboratories then discussed the endpoints for HIV-associated adipose redistribution syndrome (HARS) studies.

FACIAL LIPOATROPHY TREATMENT ENDPOINTS

Facial lipoatrophy is characterized by reduced subcutaneous fat (the hypodermis, for which skin thickness is the surrogate measure) and reduced fat pads in the buccal and temporal areas of the face and the orbital rim. Six studies were used to support regulatory approval of PLLA to treat facial lipoatrophy; four were conducted in Europe and two were conducted by individual investigators in the U.S. These are designated as the VEGA study;¹⁴ the Chelsea and Westminster study;¹⁵ and the APEX001, APEX002, and Blue Pacific studies [data on file, Dermik Laboratories]. Another study was presented at the 11th Conference on Retroviruses and Opportunistic Infections but was not used for approval.¹⁶

Skin thickness was assessed with skin calipers and by ultrasound, using the LOGICQ 7 (General Electric) and SONOLINE® Elegra (Siemens) with transducers producing digital frequencies between 7.5 and 13 MHz. The sensitivity was 0.2 cm. Measurements by skin calipers were prescribed on a visual template (Figure 1) and were reviewed by the FDA. Nonetheless, inter-investigator variability in measurements was wide.

Figure 1. Skin Thickness Isolation Points



In the VEGA study, 14 patients were treated every 2 weeks for four treatments (days 0, 15, 30, and 45) with a fifth treatment (day 60) if needed. The mean increases in facial fat were 5.2, 6.4, 7.2, 7.2, and 7.0 mm at weeks 8, 24, 48, 72, and 96, respectively. All mean values were statistically significant ($p < 0.001$). In the Chelsea and Westminster study,¹⁵ left and right nasolabial measurements and left and right cheek measurements were 2.4 to 2.7 mm at baseline and had improved to 6.3 to 6.7 mm at week 12, after three injections.

In the Blue Pacific study, results were highly investigator dependent, despite detailed instructions for measurement procedure. For example, baseline means of 5 mm with increases to 10 mm while were observed at one site, compared to baseline means of 7 mm with increases to 16 mm at another site. Methods used to record the hypodermis and fat pads included CT scan or MRI, triaxial photogrammetry for surface measurements, and standard photographs. The Lafaurie study used three-dimensional surface photogrammetry (3dMD LLC®, London, England) from which the volume of hypodermis and fat pads were back-calculated.¹⁶ The method

is laborious and has not been validated, although a cumulative decrease in facial atrophy was apparent at 2 months and 6 months after treatment. Alignment of the ultrasound measurements with the serial standard photographs for one subject from the VEGA study showed a good correlation of significant change at weeks 27 and 104.

Assessment of facial atrophy treatment effects requires holistic techniques that are reproducible, relevant to the desired effect to be measured, and easy for clinicians to use. The psychosocial impact of lipodystrophy and any improvement needs to be assessed, as well, by using quality-of-life questionnaires that measure body self-image, emotional distress, and the impact of the condition on work.

What are the best methods for establishing baselines and treatment response? Skin thickness may be a misleading measurement if there are other changes that compensate for overall thickness but are not attributable to the treatment. Serial photographs need to be standardized as to overall view, lighting, and facial regions. The best method of measuring psychosocial impact is also uncertain. The Medical Outcomes Study--Short Form (SF-36) is the best known and considered the gold standard for measuring health status (available at <http://www.sf-36.org>).¹⁷ Other measures used in prospective studies include the Hospital Anxiety and Depression Scale (available at (http://www.nfer-nelson.co.uk/catalogue/catalogue_detail.asp?catid=98&id=1125)),¹⁸ Perception of Body Thinness (a visual analog scale), and other visual analog scales. The most widely used body image measure is the Appearance Scale of the Multidimensional Body Self-Relations Questionnaire (available at <http://body-images.com/assessments/order.html>). Other body image tools are Body Image Quality of Life and the Situational Inventory of Body Image Dissatisfaction (short version).^{19,20}

Dermik Laboratories is working on a new scale, the Facial Appearance Inventory, to measure feelings about facial appearance in different situations. It is a 7-point Likert scale (-3/very negative to +3/very positive) with 35 questions that ask the patient to assess his/her feelings over the previous 3 months in a variety of situations. It is still being validated.

In the case of PLLA, the filler had been used previously in cosmesis for other indications. It was pursued in Europe for HIV-associated facial lipoatrophy based on an investigator-initiated IND. To fulfill European marketing requirements, preclinical animal data and two clinical trials were submitted for regulatory review. In the clinical trials, the rate of increase in facial fat was patient-specific; treatments occurred at 2-week intervals over several weeks to attain the desired effect. Selection of patients for the trials was based on an unvalidated 4-point scale on the need to treat, as applied by the investigator. Patients scoring at the extreme of the scale qualified for trial inclusion.

LIPODYSTROPHY TREATMENT ENDPOINTS

To pursue clinical development of a treatment, the pharmaceutical company determines whether several conditions favorable to the effort are met. These include:

- prevalence of the clinical condition (For instance, will new antiretroviral drugs coming to market reduce the incidence of lipodystrophy?)
- unmet clinical need
- feasibility of diagnosis
- availability of candidate therapy
- feasibility in assessing safety and efficacy of the candidate therapy (e.g., the number and type of blood draws that will be required)
- optimal dosage and duration of treatment for the candidate therapy
- availability and efficacy of other therapies for the target condition

- likelihood of obtaining registration

Two examples of drugs previously approved to treat HIV-associated physical abnormalities are alitretinoin topical gel (Panretin®) for cutaneous Kaposi's sarcoma and r-hGH (somatropin for injection) (Serostim®) for HIV-associated wasting/cachexia. Alitretinoin reduced stigmatizing lesions, especially facial ones, but did not alter the outcome of the Kaposi's sarcoma patients. R-hGH increased weight and lean body mass and also increased physical endurance as measured on a stationary bicycle or treadmill. Both drugs improved self-reported quality of life.

Drugs under consideration to treat abnormal fat distribution in HIV patients include PLLA for facial lipoatrophy, r-hGH for truncal lipohypertrophy in HARS, insulin-sensitizing agents for diabetes, and statins and fibrates for dyslipidemia. Features of HIV lipodystrophy that can be targeted for treatment include:

reduced facial fat, subcutaneous limb fat, and other subcutaneous fat;

increased VAT, dorsocervical fat ("buffalo hump"), and other areas of fat; and

diabetes mellitus, impaired glucose tolerance, and/or dyslipidemia.

HIV lipodystrophy syndrome may involve any or all of the conditions and patients often are affected by several of them. Whether HIV lipodystrophy is truly one syndrome or a number of syndromes remains controversial.^{2,3,21} The concept of HIV-associated adipose redistribution syndrome (HARS), clinically characterized primarily by increased trunk fat, including excess VAT, often associated with excess dorsocervical fat, metabolic abnormalities, and subcutaneous lipoatrophy¹¹ has been proposed to aid in differentiating HIV patients with abnormal excess of VAT from those without it.

In HIV-negative individuals, increased visceral adiposity may be diagnosed by a CT or MRI scan of the abdomen, or it may be estimated anthropometrically by measuring an increased waist circumference and an increased waist-to-hip ratio. In

this case, visceral adiposity is also associated with metabolic disorders (e.g., dyslipidemia and insulin resistance) and an increased risk of cardiovascular disease.²²⁻²⁵ Visceral adiposity is seen in patients with r-hGH deficiency; treatment with r-hGH leads to reduction of visceral adiposity.²⁶

The same syndrome and risks occur in HARS patients.^{2,11,21} In addition, the presence of increased dorsocervical fat is associated with respiratory problems (breathlessness, sleep apnea), decreased mobility of the neck and trunk, and stigmatizing appearance. Problems with appearance may cause psychological problems and poor adherence to prescribed antiretroviral drugs.

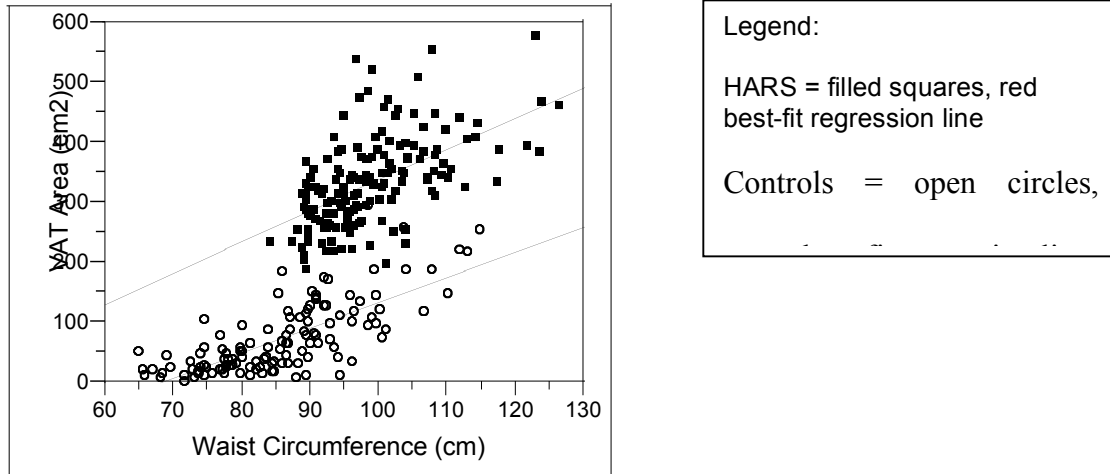
Minimum waist circumferences and waist-to-hip ratios were developed to help select HIV-positive men and women with excess visceral adiposity for clinical trials (Table 1).²⁷

Table 1. Excess Visceral Adiposity

	Waist Circumference (in centimeters)	Waist-to-hip Ratio (in centimeters)
Males	>88.2	>0.95
Females	>75.3	>0.90

At a given waist circumference, HARS patients with increased waist circumferences and waist-to-hip ratios had increased visceral adiposity compared to healthy controls (Figure 2).^{27,28}

Figure 2. Relationship of Waist Circumference to Visceral Adipose Tissue (VAT)



Growth hormone therapy was found to reduce VAT and dorsocervical fat pads and to improve the lipid profile after 24 weeks of therapy. In several studies, r-hGH decreased VAT more than abdominal subcutaneous adipose tissue, decreased trunk fat more than limb fat, improved patient-reported quality of life and body image distress, decreased total and non-HDL cholesterol levels, and increased HDL cholesterol levels.^{9,11,29-35} However, at a dose of 6 mg/day, adverse events (e.g., hyperglycemia, arthralgia) were seen more frequently in HARS patients than had been seen in patients with HIV-associated wasting.^{9,36} As a result, current studies evaluating r-hGH for the treatment of lipodystrophy are using lower doses and evaluating moderate dose induction therapy followed by low-dose maintenance therapy.^{10,11,33,35,37}

These studies have revealed several issues to be addressed in the design of clinical trials for lipodystrophy:

- 1) Clinicians need training in anthropometry, although standardized anthropometric measures have been successfully employed in clinical research, including large multicenter studies sponsored by the National

Institutes of Health (e.g., The National Health and Nutrition Survey [NHANES],³⁸ The Fat Redistribution and Metabolic Change in HIV Infection [FRAM] study,^{39,40} HIV studies within the AIDS Clinical Trials Group [ACTG] and Community Programs for Clinical Research on AIDS [CPCRA]) and large multicenter international trials).

- 2) There are no standards for ascertaining truncal and dorsocervical fat accumulation by serial photography, and attempts to use this technique for endpoints have failed.
- 3) CT and MRI scans perform very well for assessing regional body fat content, including qualifying VAT, but their expense may preclude their widespread use.
- 4) Questionnaires to measure the impact of treatment on quality-of-life and self-image need to be validated and approved by the FDA.

Questionnaires validated in English (e.g., those used in the r-hGH and HARS studies) need to be translated and validated in languages other than English if used with non-English-speaking subjects.

Facial lipoatrophy and HARS constitute new clinical entities in HIV with unmet clinical needs. Lipodystrophy syndrome presents new challenges to clinical development and drug approval processes as well as to health care delivery.

DISCUSSION

Disparate results may be obtained when comparing subjective to objective measurements, as illustrated by the MITOX study. In this open-label study investigating the effect of switching from stavudine (d4T) or zidovudine (ZDV) to abacavir on lipodystrophy.⁵ Patients displayed lipodystrophy in two regions of the body, based on subjective assessment, and were randomly assigned to continue d4T (or ZDV) or to switch to abacavir. After 24 weeks, 44% of the control group opted to switch to abacavir, as permitted in the study design. Patients were evaluated every 12 to 24 weeks by objective measurements (DEXA and CT scans) and subjective measurements (patient self-report questionnaires). Data were analyzed as intent-to-treat based on random assignment at entry. Change in limb fat in patients who switched to abacavir at day 0 was +11% at week 24 and +39% (+1.38 kg) at week 104. In contrast, at week 24, no significant limb fat changes were observed in patients who remained in the control group for the entire study; at week 104, limb fat increased by only +2% at week 24 (considered within the variability of the tests) and +6% (0.24 kg) at week 104. Patients who switched to abacavir at week 24 increased limb fat by 15% (0.55 kg) by week 104. In subjects on abacavir from day 0, right thigh fat as measured by CT scan showed a peak increase at week 72, while right leg fat as measured by DEXA scan continued to increase through week 108. Although the improvement in limb fat was progressive throughout the study for these patients, subjectively they thought they had lost limb fat or had no improvement following the week 48 assessment.

The effect of rosiglitazone (Avandia®) on lipodystrophy was investigated in a placebo-controlled, randomized trial.⁴¹ A single operator performed all imaging in this single site study, thus eliminating inter-operator variability. Limb fat as measured by DEXA scan was plotted against malar subcutaneous tissue thickness as measured by ultrasound. No correlation was found between the two (P=0.44). Although this study did not show improvement in lipodystrophy using DEXA,

other studies have shown positive results using this technique. This discrepancy has yet to be explained. One potential explanation is that thymidine analogues may act on peroxisome proliferator-associated receptors-gamma [PPAR-gamma] to cancel any benefit from rosiglitazone. If this is the case, the rosiglitazone studies may need to be repeated in study designed to include discontinuation of nucleoside-analogue reverse transcriptase inhibitors [NRTIs].⁴²

Objective measurement and statistical significance are important, however, ultimately, results must be meaningful to the patient. Agreement between objective and subjective measurement does not constitute clinical validation of the endpoints; however concordance between objective and subjective measurements lends support to the clinical relevance of the results for the particular study. Multiple measurements with statistical correlation are needed for validation. Clinically supportive data are needed until questionnaires are validated, which means that dual primary endpoints that include both objective and subjective endpoints will be required in the interim. If an objective improvement were documented in a clinical trial with no corroborating subjective improvement, the FDA would present the study results to an advisory committee. The approval of a lipodystrophy drug that lacked evidence for clinical improvement would be more difficult.

The MITOX study was not placebo-controlled. A placebo-control arm of a study is needed to adequately evaluate new treatments in most cases, although it would be more difficult for studies of interventions such as PLLA. Placebo controls are particularly important in studies using subjective measurements as endpoints. The help of psychologists and psychosocial researchers is needed to design and validate sensitive subjective instruments. The FDA is working on obtaining more expertise in evaluating questionnaires.

The FDA advisory committee on obesity trials discussed the need for placebo-controlled studies, but the use of self-report questionnaires was not discussed.

Philosophically, the requirements imposed on lipodystrophy trials should be the same as those used for obesity trials. However, there are many other adverse outcomes that can be followed in clinical trials of treatments for obesity or lipodystrophy. In obesity studies, the correlation between VAT loss and total body weight loss might be useful for overriding a lack of subjective data, but the FDA does evaluate quality of life as well as objective results. Serono Laboratories worked closely with the FDA to develop an acceptable quality-of-life measure for its r-hGH studies.

Subjective measures are difficult to reproduce across studies. In the MITOX study, self-assessment was significantly different between the abacavir arm and the d4T or ZDV arm at 24 weeks, but statistical significance was lost thereafter, since patients in both groups perceived improvement. The self-assessment may not have been sufficiently sensitive, since it used a scale of 0 to 3 to record subjective improvement.

The definition of the degree of fat loss or gain prior to and after treatment will be important, furthermore, to support coverage of treatment by insurance companies. Often, patients do not have presynndrome measurements that will objectively demonstrate the need to initiate treatment or enter a clinical trial.

FACIAL LIPOATROPHY CLINICAL TRIAL CONSIDERATIONS

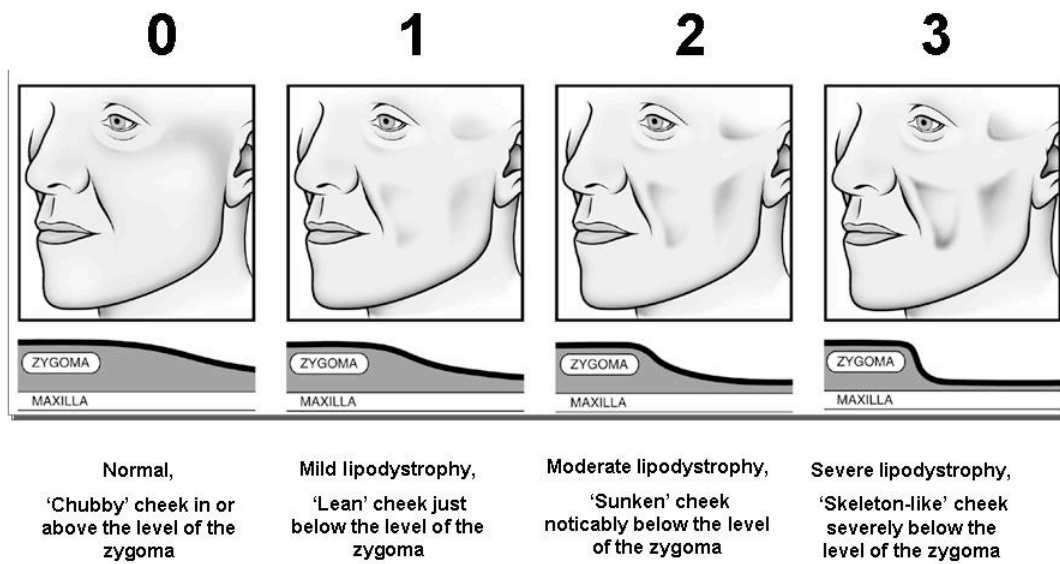
Objective data documenting facial lipoatrophy prior to entry to a clinical trial are usually unavailable. The issue of access to PLLA in clinical trials and for approved treatment in the UK National Healthcare System raised concern about how to limit what was originally perceived as a high-demand and potentially unlimited service. These concerns were addressed by using a simplified four-stage cartoon (Figure 3, provided by Chelsea and Westminster Hospital, London, England). Based on current experience, lipoatrophy may not require exact measurement of every

millimeter of dermal thickness. Furthermore, the demand for the service appears to be limited to patients with moderate to severe lipoatrophy. In the U.S., however, it may be necessary to define the degree of lipoatrophy against which to measure improvement to obtain insurance coverage of the treatment.

Figure 3: Facial Lipoatrophy Scale

Chelsea and Westminster Hospital, London

Lipoatrophy Scale



Documentation of both subjective and objective improvement of facial lipoatrophy in clinical trials is needed for approval. From the patient and the clinician perspective, such exacting standards will not be needed. The change is usually immediately visible – and may be dramatic -- with fillers. This fact alone may result in subjective overstatement of the improvement.

Standardization across trials is another issue for clinical studies. For instance, should facial lipoatrophy be measured in terms of skin thickness or regional volume? Objective measurements include direct measures of volume (e.g., CT scan, MRI scan) and inferred measures of volume (e.g., DEXA, anthropometry). Tables of population normal values for ultrasound and other methods of measurement need to be developed.

The durability of effect will be important and will vary depending on the frequency of treatments, the method used to assess change, and the degree of change. The cost of the treatments may also affect patient response to the duration of treatment. From the patient perspective, the effect does not have to be permanent to be of benefit. Temporary or removable procedures may be of interest in the event that progress in our understanding of the etiology of lipoatrophy is sufficient to allow the reversal of the syndrome. The safety endpoints and length of follow-up required to maintain beneficial effects may depend on the type of intervention or drug.

Once a beneficial treatment effect has been demonstrated, additional studies might not need a placebo control, depending on the type of study. For the patient, total appearance is the most important outcome of treatment for facial lipoatrophy. Restoration to self-perceived normal should be the goal. Future studies should clarify the role of buccal fat pads in relation to subcutaneous fat in facial lipoatrophy.

PERIPHERAL LIPOATROPHY CLINICAL TRIAL CONSIDERATIONS

The FDA has not taken a position on required entry criteria for peripheral lipoatrophy studies. Entry to clinical trials could be based on “staging” for the degree of fat loss; however, this will be difficult in heterogeneous patient populations. Questionnaires have not been helpful in defining peripheral lipoatrophy. Possible objective measures include (1) total-body MRI, which is

expensive and problematic for regional interpretation; (2) CT scan and regional MRI, which provide a direct measure of area and volume; (3) DEXA scan and anthropometry, which provide indirect measures of area and volume; and (4) bioelectrical impedance analysis (BIA), which is a total and not a regional measure but has the potential advantage of being reimbursable by Medicare.

Currently, population normal-value distributions have not been established. Anthropometry varies by population; for instance, skin thickness normal values vary based on race and skin type. Although DEXA scans are FDA-approved only for bone density studies, they can still be used for lipodystrophy studies, the way viral load tests were used in clinical trials before they were FDA-approved. In the rosiglitazone and MITOX studies,^{5,41} peripheral lipoatrophy was defined based on DEXA scores, with 80% and 85% to 90% of patients, respectively, meeting those criteria at entry. DEXA scans are the primary objective measure in lipodystrophy studies. A limb fat measure of less than 8 kg or a 25% loss in peripheral fat would be a reasonable entry criterion.

Early clinical trials should treat patients with the greatest peripheral lipoatrophy first, since these patients are at the highest risk for metabolic abnormalities. General population DEXA tables list peripheral limb fat in the range of 8 to 10 kg, while those with lipoatrophy have 5 to 5.5 kg or less of peripheral fat. A change of two standard deviations in DEXA score or an increase of 15% in limb fat is a reasonable target outcome; if lower cut-offs are used, longer follow-up will be needed. However, in multicenter studies, the variability due to DEXA machines and the lack of normative population data will limit the objectivity of the data. The baseline values also affect the degree of change that would suffice for successful outcome. A 0.5 kg gain in peripheral fat may not be associated with a metabolic benefit (in fact, a 39% gain over 2 years did not correlate with metabolic changes in the MITOX study), and a 0.5 kg change is less meaningful in patients with higher baseline limb fat. If an absolute weight is used as an endpoint, a graduated scale

may be needed to assess benefit. A percentage gain in limb fat may be a more reasonable endpoint.

It is hard to demonstrate subjective benefit in peripheral lipoatrophy studies, although, from a patient perspective, any cumulative improvement would be viewed positively. Currently, there is no correlation between objective and subjective measures. Patients may find peripheral lipoatrophy to be less of a problem than facial lipoatrophy, visceral adiposity, and dorsocervical fat deposition, however, discomfort is an issue for patients with significant peripheral lipoatrophy. Therefore, a small percentage gain in limb fat and an improvement in metabolic parameters (e.g., cholesterol levels, glucose intolerance) would be a benefit in patients with severe peripheral lipoatrophy. A more substantial gain in limb fat would be required to indicate benefit in patients with moderate peripheral lipoatrophy. However, the study must show that visceral adiposity and metabolic parameters are not worsened by the treatment.

VISCERAL ADIPOSITY CLINICAL TRIAL CONSIDERATIONS

Entry criteria for visceral adiposity trials should be based on objective measures, such as CT or MRI scans that directly measure VAT, or DEXA scans, MRI scans, and anthropometry that indirectly measure VAT. Given the published correlation between reductions in body weight, total fat mass, and VAT,⁴³ early central adiposity studies should recruit patients with body mass indices in the overweight or obesity range. The National Heart Lung and Blood Institute (NHLBI) defines obesity as a body mass index of 30 kg/m² or more and overweight as a BMI of 25 to 29.9 kg/m².⁴⁴

Previous studies have shown greater sensitivity and specificity when two anthropometric parameters (i.e., waist circumference and waist-to-hip ratio) are used to estimate visceral adiposity in HIV-infected patients rather than one

parameter alone (e.g., waist circumference). Waist circumference increases less in HIV-associated visceral adiposity than in syndrome X or metabolic syndromes in non-HIV-infected patients because HIV-infected patients with excess VAT often lose subcutaneous abdominal fat.

The patients who entered the first phase II and III trials of r-hGH in HARS (protocols that were reviewed by and accepted by the FDA) were either overweight or obese. In the phase II trial, the mean BMI was 27 kg/m². However, NHLBI recognizes that BMI alone has limitations, and that abdominal fat may be an independent cardiovascular risk factor when BMI is not markedly increased. Because of this, obesity was not a required entry criterion in either the phase II or phase III studies of r-hGH in HARS.

The NHLBI also recommends measuring waist circumferences in addition to measuring BMI when evaluating a patient's abdominal fat as a part of risk assessment. However, as noted above (and as illustrated in Figure 2), there are limitations to using waist circumference in VAT estimation in HIV-positive patients. According to NHLBI, a high-risk waist circumference for men is >102 cm. In Figure 2, about half the men with HARS in the phase II r-hGH study did not meet that criteria, yet almost all of the men with HARS had VAT areas that exceeded the mean VAT of the high-risk control men (those without HIV infection) who had waist circumferences >102 cm. Similarly, in another analysis, although men with HARS did not all have a BMI in the obesity range, they all had much more VAT than the mean for healthy, obese controls.²⁸ Hence, HIV patients who met the anthropometric entry criteria (which estimate increased VAT) and who are either overweight or obese tend to have profoundly high levels of VAT compared to HIV-negative controls with similar waist circumferences or BMI.

In the completed phase II STARS study,^{11,34} the primary endpoints were reduction in visceral adiposity and improvement in a validated, sponsor-derived quality-of-

life questionnaire score. For drug approval, both of these endpoints would need to show improvement in phase III studies, along with an adequate durability of effect and a favorable risk-benefit profile. The FDA is looking for the induction and maintenance of a 5%-10% decrease in visceral adiposity, based on the “5% guidelines” for obesity studies and the 10% decrease in visceral adiposity previously reported in HIV patients treated with r-hGH during the phase II trial.¹¹ A 5% decrease might be acceptable, depending on baseline values. It is unclear whether a decrease in VAT alone, without associated positive metabolic changes (i.e., an improvement in lipid profile and/or glucose tolerance), has any benefit in preventing cardiovascular disease. The scenario of a 10% decrease in VAT with no other positive metabolic changes would likely require review by an FDA advisory panel. From a patient perspective, a reduction in VAT is desirable even without metabolic changes.

Improvements in central adiposity (and peripheral lipoatrophy) are gradual, as demonstrated in the MITOX study. There may be no way to accurately subjectively assess such gradual change except, perhaps, in discreet time intervals or in a discreet study part (e.g., during the induction phase of an induction/maintenance study). As discussed earlier, changes in scores derived from validated quality-of-life and body self-image questionnaires are considered by the FDA to be extremely important, supportive, secondary efficacy endpoints in any trial designed to assess the efficacy of a therapeutic agent in decreasing central adiposity.

Available and potential agents to treat obesity will likely achieve a 10% reduction in body weight. The development of anti-obesity drugs and hypolipidemic agents followed similar stages of clinical study: (1) the first studies demonstrated reduced weight or lipid levels; (2) these were followed by regression studies; (3) then cardiovascular outcome was studied. Over the past four years, the FDA advisory committee has avoided mandating metabolic endpoints for obesity studies, and they have not required cardiovascular outcomes because the need for treatment has

already been established in the NHANES⁴³. However, the evaluation of metabolic endpoints (i.e., lipid profiles, glucose and insulin levels) is essential for an appropriate evaluation of safety and efficacy in central adiposity trials.

Furthermore, cardiovascular outcomes should be addressed in long-term extension studies.

If visceral fat loss is the sole endpoint, the study must show that peripheral lipoatrophy and lean tissue loss are not exacerbated by the treatment. In the phase II STARS study, mean baseline peripheral fat by DEXA was 5.5 kg. During induction, peripheral fat decreased by 0.4 kg, which was not quite statistically significant. Further clarification of this finding is part of the reason for the maintenance phase of the ongoing phase III study described above.

At the 6th International Workshop on Adverse Drug Reactions and Lipodystrophy, which began the day following the roundtable discussion, Grinspoon et al. presented a study of TH9507, a r-hGH releasing factor analog⁴⁵. This was a randomized, placebo-controlled, double-blind, multicenter study in 61 HIV-infected men and women. Patients with type II diabetes or glucose intolerance were included in the study. The waist circumferences of men (N=54) and women (N=7) had increased to ≥ 95 cm and ≥ 94 cm, respectively, and the waist-to-hip ratios were ≥ 0.94 and ≥ 0.88 , respectively. (Data on baseline VAT area were not presented in the abstract, so it is unknown how much excess VAT area these patients had or how these data would compare to patients in previously reported studies of r-hGH treatment for HARS.) Patients were treated once daily for 12 weeks with subcutaneous injections of placebo or 1 mg or 2 mg of study drug. Effectiveness was assessed using CT scans at L4-L5 to measure changes in VAT and DEXA to measure truncal fat and other body composition parameters. Changes from baseline in the 2 mg dose group were an 80% increase in IGF-I (P<0.001 versus placebo), a 1.7 kg increase in lean body mass (P<0.01 versus placebo), and a 1.1 kg decrease in truncal fat (P<0.01 versus placebo). There was no decrease in subcutaneous fat,

whereas VAT decreased 15.7% ($P < 0.05$ versus baseline) in the 2 mg dose group. The placebo group lost 5.4% (not significant) of visceral fat. The difference in VAT loss between the TH9507 group and the placebo group was not statistically significant. There was no significant change in limb fat in any group. The total cholesterol-to-HDL ratio improved in the 2 mg dose group, and both study drug groups tolerated TH9507 well. This study meets many of the clinical trial design needs discussed by the roundtable except for long-term follow-up to evaluate durability of effect and use of a validated quality-of-life body self-image instrument

Pharmacologic studies will be needed to assess drug interaction with antiretroviral agents. Sample size and duration of study will depend on whether the agent is a preventative or therapeutic one.

DORSOCERVICAL FAT PAD CLINICAL TRIAL CONSIDERATIONS

Entry criteria to clinical trials should be based on patient and physician agreement on the need for treatment. A requirement for symptomatic status would adversely affect enrollment, although defined symptoms might be relevant entry criteria for topical treatments. Other measures include changes in anthropometrics and cartoon scores to evaluate changes prior to and after study entry. Any accompanying symptoms, such as apnea, headache, and neck and back stiffness or pain, should be followed as a study endpoint. Specific quality-of-life questionnaires would benefit these studies.

CONCLUSIONS

The roundtable participants agreed that for purposes of defining entry criteria and measuring response to therapies for lipodystrophy, there are four distinct therapeutic types: facial atrophy, peripheral atrophy, visceral adiposity, and dorsocervical fat pads.

GENERAL CONSIDERATIONS IN CLINICAL TRIAL DESIGN

- Clinical trials should be designed as prospective, randomized studies with randomly assigned treatment lasting for at least 6 months.
- Longer periods of randomly assigned treatment may be needed as more treatments become available.
- Drug studies that rely on quality-of-life measures should have a placebo control.
- Endpoints should be comparable across studies, such as standardized photography compared by means of a standardized grading scale to document changes in facial lipoatrophy.
- All endpoint measures, including quality-of-life scales, should be obtained with validated methods.

FACIAL LIPOATROPHY

- Entry into a clinical trial should be decided by patient and physician based on subjective determination of the presence of facial lipoatrophy not caused by HIV wasting.
- Effectiveness of treatment should be based on (1) objective measurements of fat restoration, e.g., by ultrasound and photograph; and (2) subjective determination of satisfactory improvement on the part of the patient and

physician. Durability of response should be assessed with at least 2 year studies.

- Safety of treatment will be assessed on a case-by-case basis and dependent on the class of drug or type of intervention.

PERIPHERAL LIPOATROPHY

- Entry into a clinical trial should be decided by patient and physician, most likely based on a subjective determination of peripheral fat loss and, if possible, an objective DEXA measurement indicating less than 8 kg of peripheral limb fat or a 25% loss of limb fat compared to population normal values (although normal values are not available for all population types).
- Effectiveness of treatment should be based on objective DEXA measurements. The percentage of increased fat that will indicate effectiveness of a treatment will depend on the baseline value.
- Safety evaluations should demonstrate no worsening of visceral adiposity or metabolic parameters (e.g., lipid profiles or glucose intolerance).

VISCERAL ADIPOSITY

- Entry into a clinical trial should be based on objective waist circumference and waist-to-hip ratio measurements and, to a lesser extent, on patient and physician selection based on a subjective determination of increased truncal fat. Early trials should recruit subjects with body mass indices in the overweight or obesity range.
- Effectiveness of treatment should be based on CT scans at the L4-L5 level (a direct measure of visceral adipose tissue [VAT] and the preferred measurement), DEXA scans (a measure of truncal fat, i.e., VAT plus subcutaneous abdominal fat), and objective anthropometry, such as waist-to-hip ratio. Induction of satisfactory efficacy after at least 3 months of

treatment and durability of efficacy after at least 6 additional months of treatment should be demonstrated. Inclusion of quality-of-life outcomes assessed by validated instruments is strongly recommended. All studies should be placebo controlled.

- Safety evaluations should demonstrate no worsening of peripheral lipoatrophy, percentage of lean body tissue, and metabolic outcomes (e.g., no worsening of baseline glucose intolerance), and, hopefully, should demonstrate an improvement in baseline dyslipidemia.

DORSOCERVICAL FAT PAD

- Entry into a clinical trial should be based on patient and physician agreement that treatment is indicated to relieve physical or psychological discomfort.
- Effectiveness of treatment should be based objectively on a reduction in the measured size of the fat pad and, in symptomatic patients, subjectively on an improved quality of life.

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REGULATORY CONSIDERATIONS FOR THE TREATMENT OF
LIPODYSTROPHY ROUNDTABLE

October 25, 2004

1:00—1:15	Welcome and Introductions	Ben Cheng
1:15—1:30	Objectives of the Roundtable Discussion	William Powderly, MD
1:30—2:00	FDA’s Perspective on Endpoints for Lipodystrophy Studies	Herbert Lerner, MD Jeffrey Murray, MD Robert Perlstein, MD
2:00—2:30	Industry’s Perspective on Endpoints for Lipodystrophy Studies	Sharon Levy, MD Norma Muurahainen, MD
2:30—2:45	Break	
2:45—3:00	Clinician’s Perspective on Endpoints for Lipodystrophy Studies	Andrew Carr, MD
3:00—4:45	Discussion	All
4:45—5:00	Next Steps	William Powderly, MD Ben Cheng

APPENDIX B: ROUNDTABLE PARTICIPANTS

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